Direct-acting antivirals for chronic hepatitis C

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[Intervention Review]

Direct-acting antivirals for chronic hepatitis C

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ABSTRACT

Background

Millions of people worldwide suffer from hepatitis C, which can lead to severe liver disease, liver cancer, and death. Direct-acting antivirals (DAAs), e.g. sofosbuvir, are relatively new and expensive interventions for chronic hepatitis C, and preliminary results suggest that DAAs may eradicate hepatitis C virus (HCV) from the blood (sustained virological response). Sustained virological response (SVR) is used by investigators and regulatory agencies as a surrogate outcome for morbidity and mortality, based solely on observational evidence. However, there have been no randomised trials that have validated that usage.

Objectives

To assess the benefits and harms of DAAs in people with chronic HCV.

Search methods

We searched for all published and unpublished trials in The Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, LILACS, and BIOSIS; the Chinese Biomedical Literature Database (CBM), China Network Knowledge Information (CNKI), the Chinese Science Journal Database (VIP), Google Scholar, The Turning Research into Practice (TRIP) Database, ClinicalTrials.gov, European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trials Registry Platform (www.who.int/ictrp), the Food and Drug Administration (FDA) (www.fda.gov), and pharmaceutical company sources for ongoing or unpublished trials. Searches were last run in October 2016.

Selection criteria

Randomised clinical trials comparing DAAs versus no intervention or placebo, alone or with co-interventions, in adults with chronic HCV. We included trials irrespective of publication type, publication status, and language.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our primary outcomes were hepatitis C-related morbidity, serious adverse events, and health-related quality of life. Our secondary outcomes were all-cause mortality, ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy, hepatocellular carcinoma, non-serious adverse events (each reported separately), and SVR. We systematically assessed risks of bias, performed Trial Sequential Analysis, and followed an eight-step procedure to assess thresholds for statistical and clinical significance. We evaluated the overall quality of the evidence, using GRADE.

Main results

We included a total of 138 trials randomising a total of 25,232 participants. The trials were generally short-term trials and designed primarily to assess the effect of treatment on SVR. The trials evaluated 51 different DAAs. Of these, 128 trials employed matching placebo in the control group. All included trials were at high risk of bias. Eighty-four trials involved DAAs on the market or under development (13,466 participants). Fifty-seven trials administered DAAs that were discontinued or withdrawn from the market. Study populations were treatment-naive in 95 trials, had been exposed to treatment in 17 trials, and comprised both treatment-naive and treatment-experienced individuals in 24 trials. The HCV genotypes were genotype 1 (119 trials), genotype 2 (eight trials), genotype 3 (six trials), genotype 4 (nine trials), and genotype 6 (one trial). We identified two ongoing trials.

We could not reliably determine the effect of DAAs on the market or under development on our primary outcome of hepatitis C-related morbidity or all-cause mortality. There were no data on hepatitis C-related morbidity and only limited data on mortality from 11 trials (DAA 15/2377 (0.63%) versus control 1/617 (0.16%); OR 3.72, 95% CI 0.53 to 26.18, very low-quality evidence). We did not perform Trial Sequential Analysis on this outcome.

There is very low quality evidence that DAAs on the market or under development do not influence serious adverse events (DAA 5.2% versus control 5.6%; OR 0.93, 95% CI 0.75 to 1.15 , 15,817 participants, 43 trials). The Trial Sequential Analysis showed that there was sufficient information to rule out that DAAs reduce the relative risk of a serious adverse event by 20% when compared with placebo. The only DAA that showed a lower risk of serious adverse events when meta-analysed separately was simeprevir (OR 0.62, 95% CI 0.45 to 0.86). However, Trial Sequential Analysis showed that there was not enough information to confirm or reject a relative risk reduction of 20%, and when one trial with an extreme result was excluded, the meta-analysis result showed no evidence of a difference.

DAAs on the market or under development may reduce the risk of no SVR from 54.1% in untreated people to 23.8% in people treated with DAA (RR 0.44, 95% CI 0.37 to 0.52, 6886 participants, 32 trials, low quality evidence). Trial Sequential Analysis confirmed this meta-analysis result.

Only 1/84 trials on the market or under development assessed the effects of DAAs on health-related quality of life (SF-36 mental score and SF-36 physical score).

There was insufficient evidence from trials on withdrawn or discontinued DAAs to determine their effect on hepatitis C-related morbidity and all-cause mortality (OR 0.64, 95% CI 0.23 to 1.79; 5 trials, very low-quality evidence). However, these DAAs seemed to increase the risk of serious adverse events (OR 1.45, 95% CI 1.22 to 1.73; 29 trials, very low-quality evidence). Trial Sequential Analysis confirmed this meta-analysis result.

None of the 138 trials provided useful data to assess the effects of DAAs on the remaining secondary outcomes (ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy, and hepatocellular carcinoma).

Authors' conclusions

The evidence for our main outcomes of interest come from short-term trials, and we are unable to determine the effect of long-term treatment with DAAs. The rates of hepatitis C morbidity and mortality observed in the trials are relatively low and we are uncertain as to how DAAs affect this outcome. Overall, there is very low quality evidence that DAAs on the market or under development do not influence serious adverse events. There is insufficient evidence to judge if DAAs have beneficial or harmful effects on other clinical outcomes for chronic HCV. Simeprevir may have beneficial effects on risk of serious adverse event. In all remaining analyses, we could neither confirm nor reject that DAAs had any clinical effects. DAAs may reduce the number of people with detectable virus in their blood, but we do not have sufficient evidence from randomised trials that enables us to understand how SVR affects long-term clinical outcomes. SVR is still an outcome that needs proper validation in randomised clinical trials.

PLAIN LANGUAGE SUMMARY

Direct-acting antivirals for chronic hepatitis C

Background

Millions of people worldwide suffer from hepatitis C, which can lead to severe liver disease, liver cancer, and death. Numerous previous interferon-based interventions have been used for hepatitis C, but none of these interventions have proven effective on patient-centred outcomes and their use was associated with serious side-effects. DAAs are relatively new but expensive interventions for hepatitis C, and preliminary results have shown that DAAs seem to eradicate hepatitis C virus from the blood (sustained virological response) much more frequently. In addition, these agents do appear to create much less serious adverse-effects. In this Cochrane Review, we assessed the evidence on the clinical effects of DAAs for hepatitis C.

Study characteristics

We included 138 randomised clinical trials. All included trials were at high risk of bias. The 138 trials used 51 different DAAs. Of these, 84 trials assessed DAAs on the market or under development; 57 trials were on DAAs withdrawn from development or the market. Trials were conducted from 2004 to 2016. The trials were from all over the world including 34 different countries. We included 17 trials where all the participants had previously been treated for hepatitis C (treatment-experienced) before being included in the trial. There were 95 trials that included only participants who had not been previously treated for hepatitis C (treatment-naive). The intervention periods ranged from one day to 48 weeks with an average of 14 weeks. The combined intervention period and follow-up period ranged from one day to 120 weeks with an average of 34 weeks.

Key results

We could not reliably determine the effect of DAAs on hepatitis C-related morbidity or death from any cause. There were no data on hepatitis C-related morbidity and very few deaths occurred over the course of the trials (15 deaths/2377 direct-acting antiviral participants (0.63%) versus 1 death/617 control participants (0.16%), very low quality evidence). Based on very low quality evidence, 5.2% people treated with DAAs had one or more serious adverse events versus 5.6% participants who were untreated during the observation period. When analysed separately, simeprevir was the only direct-acting antiviral that showed evidence of a beneficial effect when assessing risk of a serious adverse event. Our analyses, however, showed that the validity of this result is questionable and that 'play of chance' might be the cause for the difference. There was not enough information to determine if there was any effect of DAAs on other clinically relevant outcomes. Our results confirm that DAAs seem to reduce the number of people who have the hepatitis C virus in their blood from 54.1% in untreated people to 23.8% in those who were treated. Because the loss of detectable hepatitis C virus in the blood stream is only a blood test, the studies could not tell what this result means in the long term.

Quality of the evidence

Due to several limitations (e.g. lack of blinding, lack of relevant data, missing data, no published protocol) we assessed the quality of the evidence in this review as very low or low quality. First, all trials and outcome results were at high risk of bias, which means that our results presumably overestimate the beneficial effects of DAAs and underestimate any potential harmful effects. Second, there were limited data on most of our clinical outcomes, that is, there were only relevant clinical data for meta-analyses on all-cause mortality and serious adverse events, and for these, data were sparse. There are no long-term trials that have assessed whether or not DAA treatment improves morbidity or mortality.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Direct-acting antivirals versus control

Direct-acting antivirals versus control

Patient or population: adults with chronic hepatitis C
Setting: any setting
Intervention: direct-acting antivirals on the market or under development
Comparison: placebo or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI) (TSA-adjusted CI)	№ of participants (trials)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	Risk with direct-acting antivirals				
All-cause mortality at maximum follow-up	2 per 1000	7 per 1000 (1 to 42)	OR 3.72 (0.53 to 26.18) (-)	2996 (11 RCTs)	⊕⊝⊝⊝ Very low[1]	It was not possible to perform Trial Sequential Analysis because of limited data and too few events
Proportion of participants with one or more serious adverse event at maximum follow-up	56 per 1000	52 per 1000 (49 to 55)	OR 0.93 (0.75 to 1.15) (TSA CI 0.71 to 1.33)	15,817 (43 RCTs)	⊕⊝⊝⊝ Very low[2]	Trial Sequential Analysis showed that the boundary for futility was crossed. This leads us to conclude that any possible intervention effect, if any, is less than 20%
Proportion of participants with no sustained virological response at maximum follow-up	541 per 1000	238 per 1000 (200 to 281)	RR 0.44 (0.37 to 0.52) (TSA CI 0.42 to 0.55)	6886 (32 RCTs)	⊕⊕⊝⊝ Low[3]	Trial Sequential Analysis showed that the boundary for benefit was crossed. This indicates that DAAs seem to decrease the risk of no sustained virological response by at least 20% if risk of bias and other threats to the validity can be disregarded

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the observed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

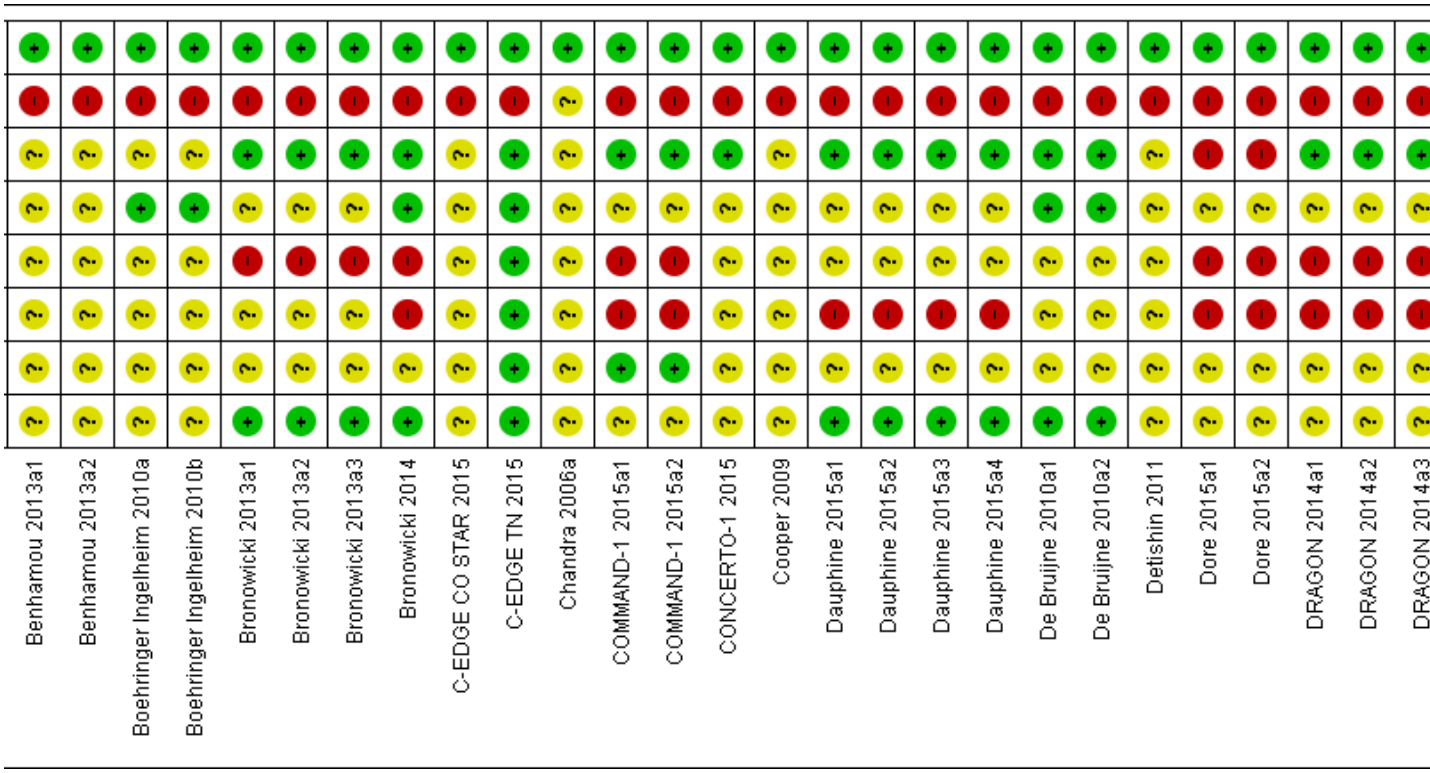
CI: confidence interval; **DAA**: direct-acting antivirals; **OR:** odds ratio; **RCTs**: randomised clinical trials; **RR:** risk ratio; **TSA**: Trial Sequential Analysis

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded two levels because of very serious risk of bias in the included trials (see Figure 1) and two levels due to very serious imprecision (none of the TSA boundaries are crossed, so the information size is too low).
[2]Downgraded two levels due to very serious risk of bias in the included trials (see Figure 1) and one level due to serious indirectness (the components of this composite outcome consisted of events with very different degrees of severity, which limits the interpretability of this outcome result).
[3]Downgraded two levels because of very serious risk of bias in the included trials (Figure 1).

Figure 1.



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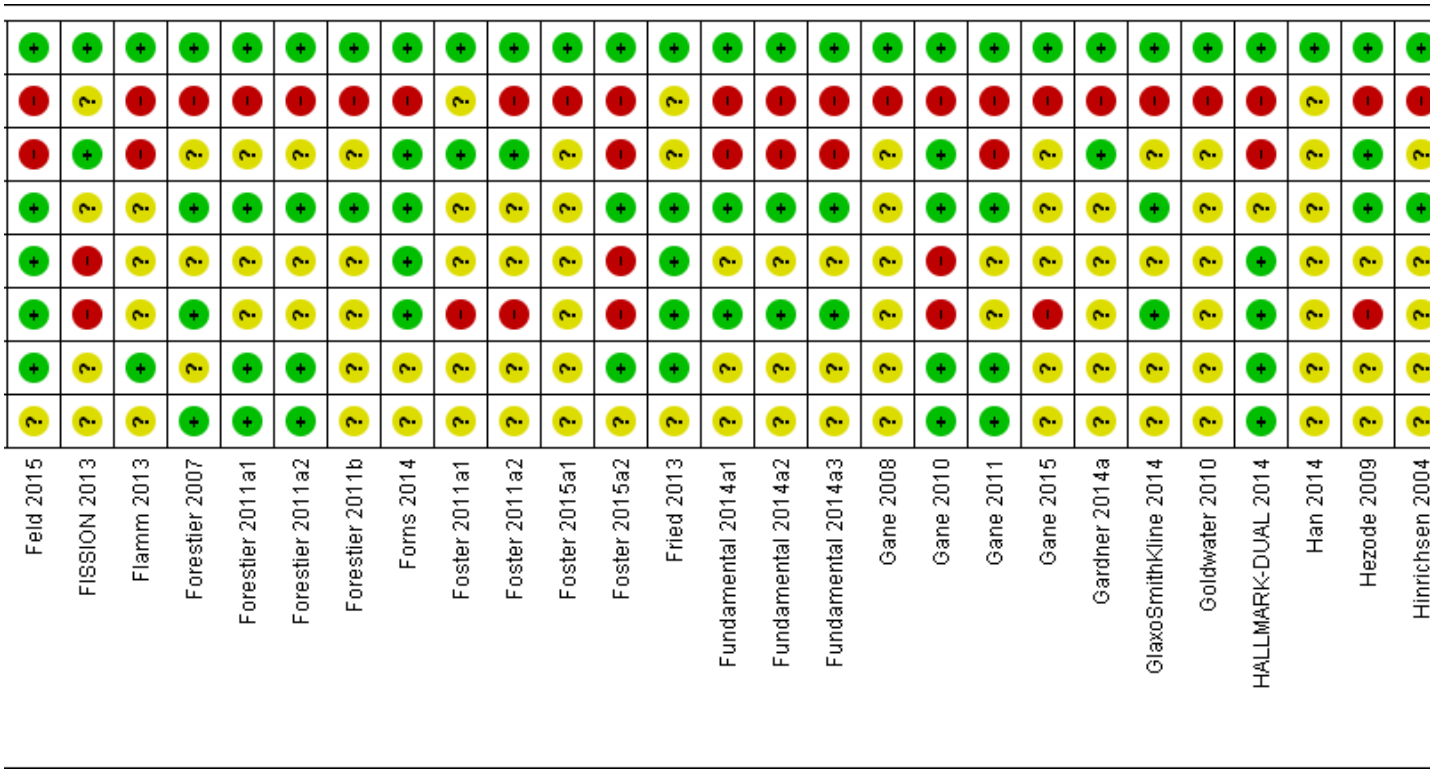

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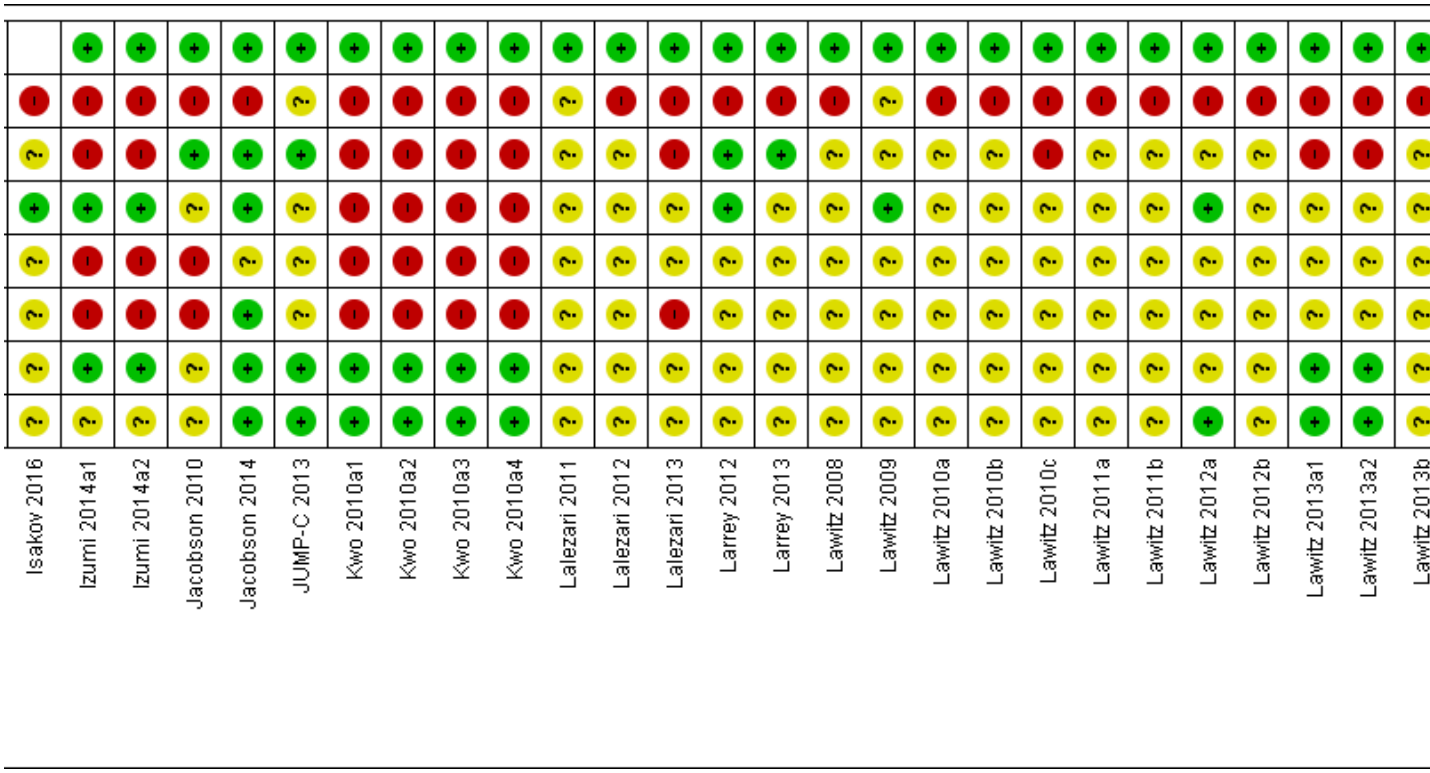

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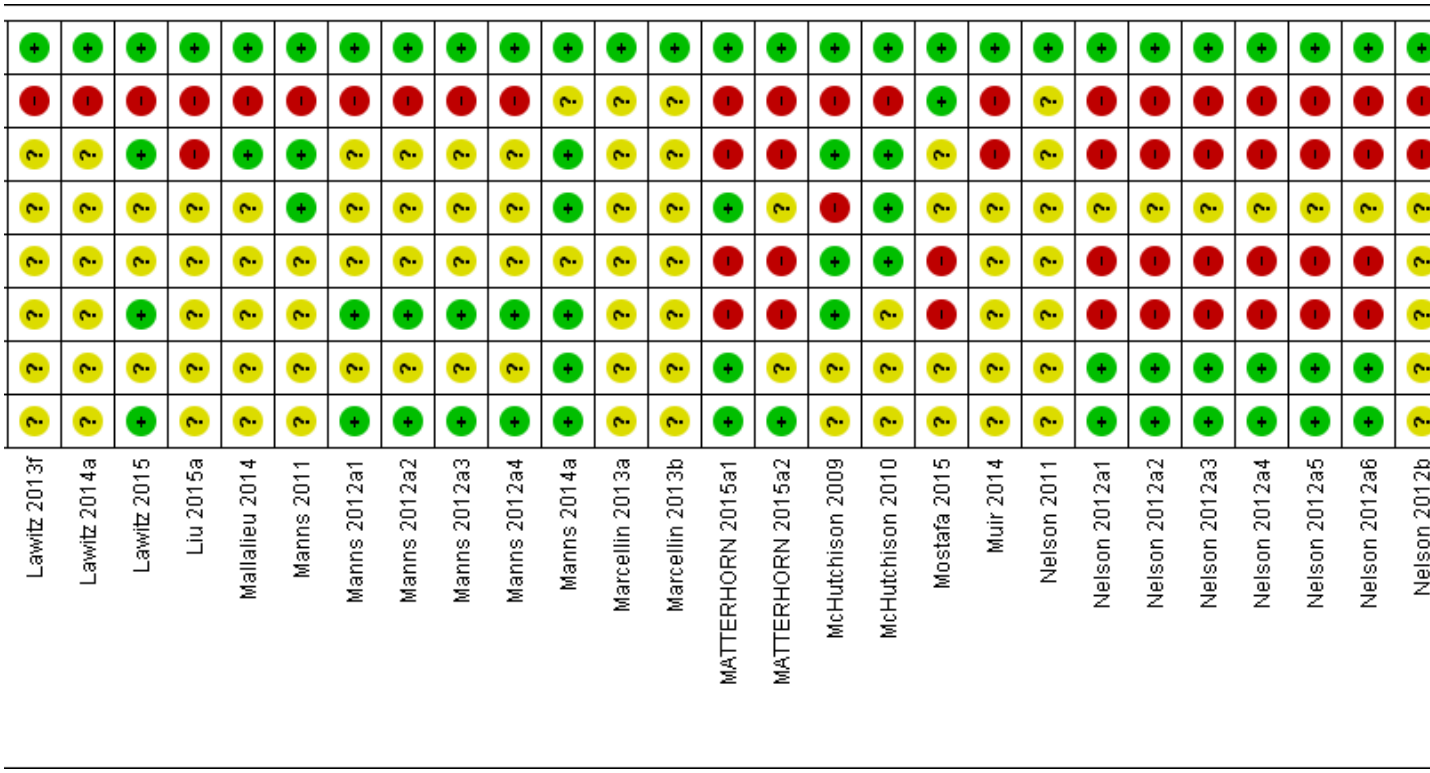

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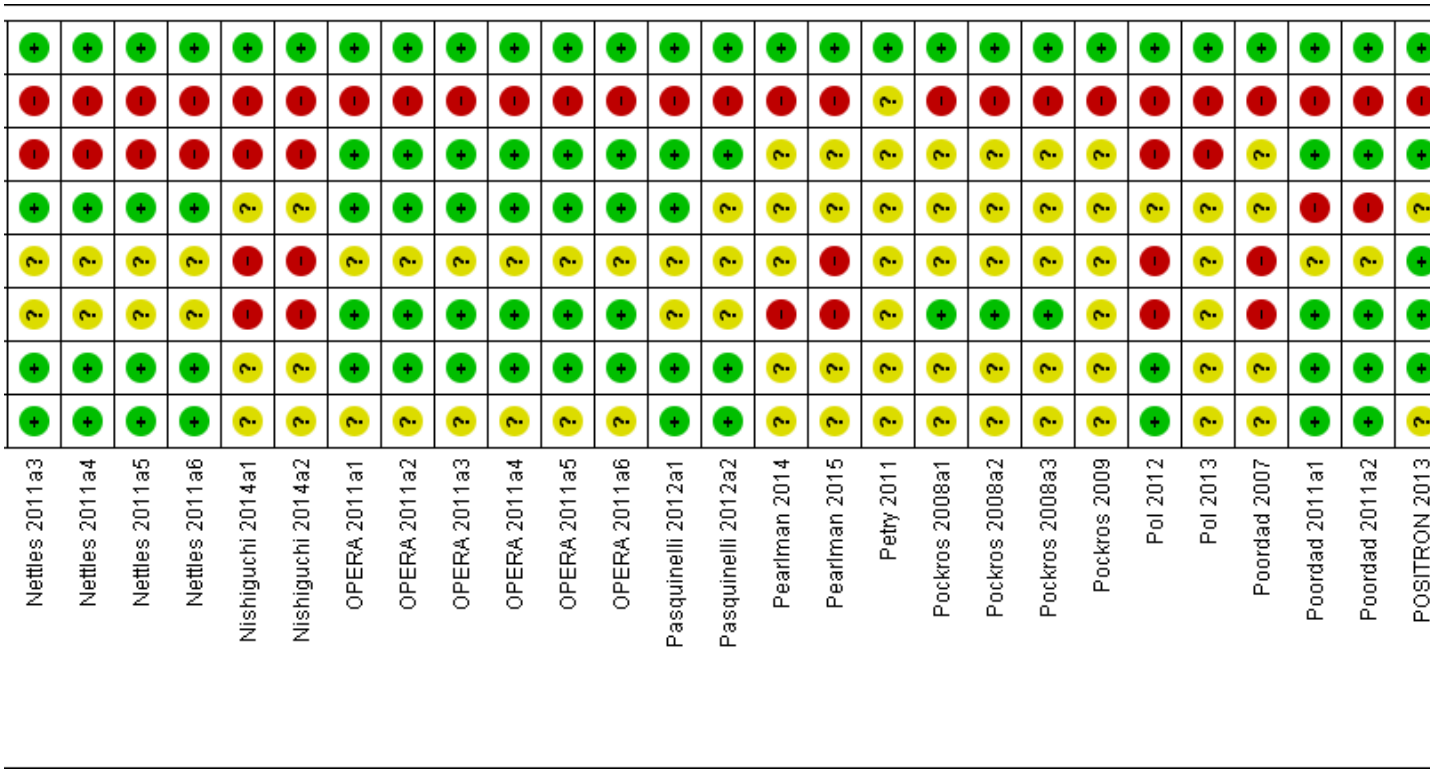

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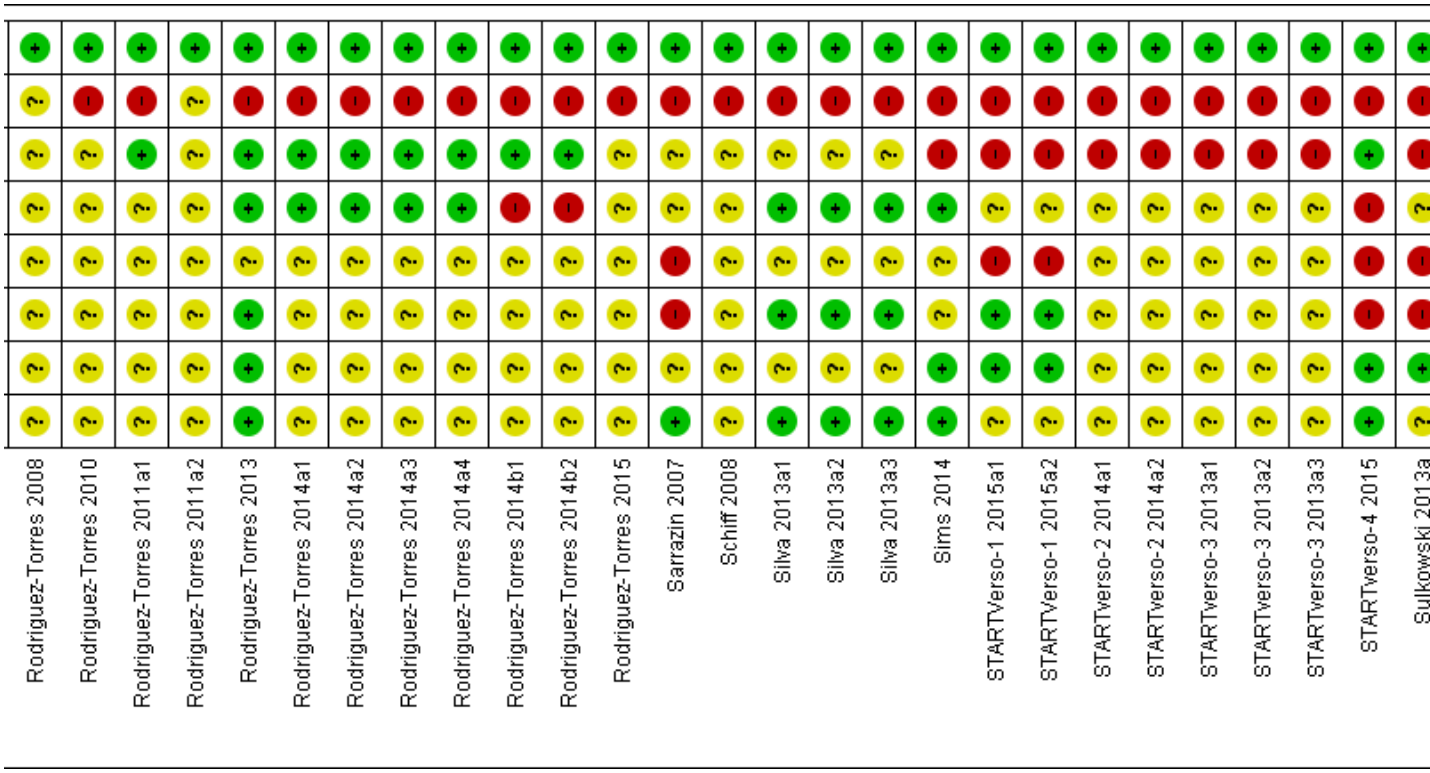

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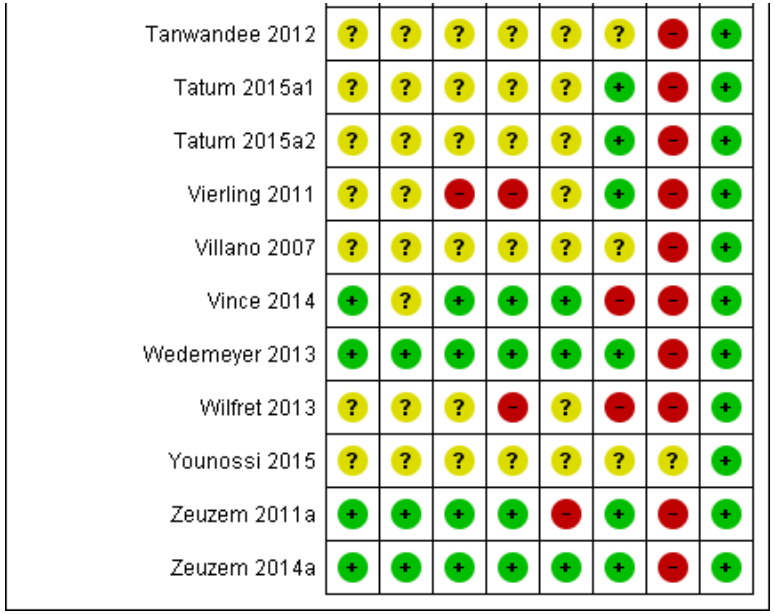

Summary of findings 2. Direct-acting antivirals withdrawn from the market versus control

Direct-acting antivirals withdrawn from the market versus control

Patient or population: adults with chronic hepatitis C
Setting: any setting
Intervention: direct-acting antivirals withdrawn from the market
Comparison: placebo or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI) (TSA-adjusted CI)	№ of participants (trials)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	Risk with direct-acting antivirals				
All-cause mortality at maximum follow-up	7 per 1000	5 per 1000 (2 to 12)	OR 0.64 (0.23 to 1.79)	3045 (5 RCTs)	⊕⊖⊖⊖ Very low[1]	It was not possible to perform Trial Sequential Analysis because of limited data and too few events

			(-)			
Proportion of participants with one or more serious adverse event at maximum follow-up	75 per 1000	108 per 1000 (91 to 129)	OR 1.45 (1.22 to 1.73) (TSA 1.16 to 1.82)	9229 (29 RCTs)	⊕⊖⊖⊖ Very low[2]	Trial Sequential Analysis showed that the boundary for harm was crossed. This shows that there is firm evidence that withdrawn DAAs increase the risk of a serious adverse event by at least 20%
Proportion of participants with no sustained virological response at maximum follow-up	586 per 1000	356 per 1000 (322 to 404)	RR 0.61 (0.55, 0.69) (TSA CI 0.42 to 0.55)	9075 (21 RCTs)	⊕⊕⊖⊖ Low[3]	Trial Sequential Analysis not performed

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the observed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **DAA**: direct-acting antivirals; **OR:** odds ratio; **RCTs**: randomised clinical trials; **RR:** risk ratio; **TSA**: Trial Sequential Analysis

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
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[2]Downgraded two levels because of very serious risk of bias in the included trials (see Figure 1) and one level due to serious indirectness (the components of this composite outcome consisted of events with very different degrees of severity which limits the interpretability of this outcome result).
[3]Downgraded two levels because of very serious risk of bias in the included trials (Figure 1).

BACKGROUND

Description of the condition

The hepatitis C virus (HCV) was discovered in 1989 and has since become recognised as the leading cause of cirrhosis and hepatocellular carcinoma (Choo 1989). Worldwide, an estimated 700,000 deaths per year can be related to HCV liver diseases and more than 115 million individuals are infected. This corresponds to a global prevalence of 1.6% (WHO 2014; MCDC 2015). Mother to child transmission of HCV has become a leading cause of paediatric infection of HCV, and up to half of the children infected with HCV acquired the HCV infection in utero (Mok 2005). In the USA, an estimated 50% of individuals with chronic HCV infection are unaware of their diagnosis (Spradling 2012). Failure to identify infected individuals has been considered to be a major bottleneck to successful control of HCV (Spradling 2012). Screening asymptomatic individuals who may have an increased likelihood of being infected with HCV could become an important step toward improving the detection and, ultimately, treatment of HCV-infected people (Spradling 2012).

HCV is a member of the family *Flaviviridae* belonging to the *Hepacivirus* genus, and is an enveloped single-stranded positive-sense ribonucleic acid (RNA) virus (Scheel 2013; Dubuisson 2014). The genome of HCV contains one open reading frame encoding a poly-protein (Scheel 2013; Dubuisson 2014). This poly-protein is processed by host and viral proteins to yield the structural (core, glycoproteins E1 and E2, and protein P7) and the nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) (Scheel 2013; Dubuisson 2014).

Classification of HCV is based on phylogeny (i.e. history of evolution) and sequence diversity, dividing HCV into seven major genotypes (Scheel 2013; Messina 2015). The geographical distribution and the prevalence of the seven genotypes varies (Scheel 2013; Messina 2015). Genotype 1 is highly prevalent, accounting for 46% of all HCV infections globally (Scheel 2013; Messina 2015). Genotype 2 has been found to dominate in West Africa, genotype 3 in South Asia and parts of Scandinavia, genotype 4 in Central and North Africa, genotype 5 in South Africa, and genotype 6 and 7 in South East Asia (Scheel 2013; Gowan 2014; Messina 2015). It has been shown that the interleukin−28 beta (IL-28B) subunit gene in the host is dramatically associated with both sustained virological response to pegylated interferon α (peg-IFNα) and ribavirin (RBV) and spontaneous viral clearance in the absence of therapy (Berger 2012).

HCV is primarily transmitted parenterally through exposure to contaminated blood (e.g. in people who inject drugs) (CDCP 1998). The signs and symptoms of HCV have been found to be largely similar across genotypes, but genotype 3 is associated with higher risks of hepatic steatosis and progressive liver disease (Scheel 2013). An infection with HCV is often asymptomatic and if the disease does not progress further to cirrhosis or give rise to cancer, it may not result in harmful events for infected people (Koretz 2015). Approximately 20% of infected people have self-limited acute hepatitis (Koretz 2015), but in the remaining 80%, the virus is not cleared, which leads to a chronic HCV infection (WHO 2014). A systematic review of 111 studies analysing the natural history of HCV infection, found that the prevalence of cirrhosis 20 years after HCV infection was 16% (Thein 2008). Other studies have reported that further progression into cirrhosis occurred in approximately 20% of HCV people but the prevalence could be even higher (Conteduca 2014; Koretz 2015; Wandeler 2015). Studies have shown varying results, but approximately 10% to 20% of the people with chronic HCV infection progress to end-stage disease (i.e., decompensated cirrhosis or hepatocellular carcinoma, not just histologic cirrhosis), which corresponds to 8% to16% of all people who are infected with HCV (Koretz 2015).

Before the appearance of DAAs, the recommended standard of care for HCV infection consisted of peg-IFN α plus RBV (Manns 2006; Brok 2009; Brok 2010; Hauser 2014). Several mechanisms of action of RBV have so far been suggested; one of the proposed mechanisms is a direct effect against the HCV RNA-dependent RNA polymerase (Clark 2012). However, given the lack of a clear understanding of the RBV mechanism, it is considered challenging to confidently classify RBV as a DAA (Clark 2012).

Treatment with peg-IFNα plus RBV, compared with other antiviral drugs, has been shown to increase the rates of sustained virological response (SVR) defined as aviraemia 24 weeks after antiviral therapy (Ermis 2015). Treatment with peg-IFNα plus RBV is associated with serious adverse events, often leading to discontinuation of the treatment, and the effects on clinically-relevant outcomes remain unclear (Brok 2010; Koretz 2013; Hauser 2014; Koretz 2015; Righi 2015). The many serious adverse events associated with IFNα plus RBV treatment has encouraged the development of new interventions, such as DAAs (Ermis 2015).

Several observational studies have shown that achieving sustained virologic response in hepatitis C seems to be associated with improved clinical outcomes (Smith-Palmer 2015). However, the SVR is a blood test and, as such, is a surrogate outcome. Since the SVR has been used universally as the primary outcome in hepatitis C treatment trials, it will be necessary to consider it in this review.

Surrogate outcomes may or may not reflect ultimate clinical outcomes and they need to be validated. Such validations cannot be accomplished only by observational evidence (Ciani 2017; Flemming 1996; Flemming 2012; Gluud 2007; Kemp 2017). Validation consists of showing that the creation of surrogate outcomes ultimately results in comparable improvements in clinical outcomes. Thus, validation requires the performance of randomised clinical trials showing that the people who obtain SVRs also have a decreased risk of hepatis C-related complications. Simply showing an association or a correlation between short-term measures and long-term clinical events does not validate a surrogate outcome. For example, people who develop SVRs have underlying characteristics that would predict that they would have better long-term outcomes even if no treatment was provided (Koretz 2015). Thus, if an observational study shows that people treated with DAAs who obtain SVRs had better outcomes than untreated (or unsuccessfully treated) people who do not obtain SVR, the explanation for the association may simply be that the SVR identified the inherently stronger population who both responded and had fewer clinical events because of their inherently better status (Ciani 2017; Flemming 1996; Flemming 2012; Gluud 2007; Koretz 2015). As indicated by Flemming 1996: "While the effect of an intervention on a biomarker does provide direct evidence regarding biological activity, such evidence could be unreliable regarding effects on true clinical efficacy measures even when the biomarker is strongly correlated with these clinical efficacy measures in natural history observations." "A correlate does not a surrogate make" (Flemming 1996). In one clinical scenario (re-

treating patients with interferon monotherapy), the SVR did fail to validate: while the treated patients did have more SVRs, they also had more morbidity and may also have had a higher all-cause mortality (Koretz 2013).

SVRs achieved with DAAs are not necessarily universal cures. A retrospective cohort study (El-Serag 2016) recently showed that the risk of hepatocellular carcinoma after obtaining SVR remains relatively high at 0.33% per year. Older age and presence of cirrhosis at the time of sustained virological response are associated with a high enough risk to warrant surveillance (El-Serag 2016). Reig 2016 has in a small observational study shown an unexpected high rate and pattern of tumour recurrence coinciding with SVR, and the authors hypothesise that disruption of immune surveillance may facilitate the emergence of metastatic clones (Reig 2016; Reig 2017). Case reports of hepatitis B reactivation have led to labelling changes for the DAAs (Wang 2017). Although SVR is widely accepted by regulatory bodies as a surrogate for long-term benefit, the results from observational studies are not definitive and validation from randomised evidence has not been confirmed (Garattini 2016; Gluud 2007; Koretz 2015).

Description of the intervention

Direct-acting antivirals (DAAs) are molecules that target specific nonstructural proteins of the virus, resulting in disruption of viral replication and thereby infection (Poordad 2012; Pockros 2015). There are four classes of DAAs, defined by their mechanism of action and therapeutic target: nonstructural proteins 3/4A (NS3/4A), protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors (Poordad 2012; Pockros 2015). Table 1 presents an overview of the different DAAs we have been able to identify.

Inhibitors of the NS3/4A protease

DAA first-generation protease inhibitors

The NS3/NS4A protease inhibitors, telaprevir and boceprevir, were approved for chronic genotype 1 HCV infection in 2011. It was shown that treating with a protease inhibitor combined with peg-IFNα plus RBV resulted in sustained virological response reaching 68% to 75% in treatment-naive (i.e. previously untreated) HCV patients and 59% to 88% in treatment-experienced patients (i.e. previously-treated HCV patients) (Scheel 2013; Righi 2015). Considerable drawbacks to the treatment with telaprevir or boceprevir include a rapid occurrence of viral resistance (Conteduca 2014), a long treatment duration (24 to 48 weeks), and an apparent increase in serious adverse events (Scheel 2013; Conteduca 2014; Righi 2015). For these reasons, and due to the development of second-generation protease inhibitors, telaprevir was removed from the market and boceprevir is no longer a recommended intervention (Righi 2015).

DAA second-generation protease inhibitors

The NS3/NS4A protease inhibitors, simeprevir and paritaprevir, are characterised by a theoretically high potency, have a low barrier to development of resistance (selection of resistant viruses), and there is cross-resistance (drug-drug interaction) among the different NS3/NS4A protease inhibitors (Roche 2015). Simeprevir was approved for administration in combination with peg-IFNα/RBV in 2013 (Ermis 2015). Simeprevir has been used against HCV genotypes 1, 2, 5, and 6 and it is generally associated with tolerable adverse effects (Conteduca 2014; Ermis 2015). The recommended treatment period with simeprevir is approximately 24 weeks. Paritaprevir is often administered in combination with low-dose ritonavir (an antiretroviral protease inhibitor of HIV/AIDS) aiming for a pharmacologic boosting effect (Pockros 2015). Paritaprevir and ritonavir are also available in combination with ombitasvir (an NS5A inhibitor, see below) and are usually administered with the NNPI dasabuvir (see below) (Pockros 2015).

DAA NS5B polymerase inhibitors and NS5A inhibitors

The NS5B polymerase inhibitors have been used against several HCV genotypes; they share a high theoretical potency and have high theoretical barrier to resistance due to the active site in NS5B, which is highly conserved across HCV genotypes (Conteduca 2014; Ermis 2015; Righi 2015). The NS5B polymerase inhibitors can be divided into two groups: NPIs and NNPIs. The first NPI approved in 2013 was sofosbuvir and it is apparently well-tolerated (Righi 2015; Roche 2015). Sofosbuvir is administered once daily for 12 weeks in combination with other drugs for HCV and has a limited cross-resistance interaction profile compared with previous DAAs (Righi 2015; Roche 2015). NNPIs, for example dasabuvir, interact with areas on the NS5B polymerase that are less critical for viral survival. Thus, the NNPIs have the lowest theoretical barrier to resistance amongst the NS5B polymerase inhibitors (Roche 2015).

Due to the theoretical low resistance barrier, NS5A inhibitors are administered with appropriate combination partners as well as protease inhibitors (Conteduca 2014). Daclatasvir, ledipasvir, and ombitasvir are all NS5A inhibitors, and in 2014 in the European Union (EU) and in 2015 in the USA, daclatasvir was approved for use in combination with other DAAs (Righi 2015; www.fda.gov).

The high cost and limited availability of DAA treatment remain as critical issues, especially in low-income countries, despite the lack of documented benefit of DAAs on patient-centred outcomes. The costs associated with DAA treatment is highly variable, but as an example, the drug cost of a 12-week course of treatment with sofosbuvir amounts to GBP 34,983 (excluding value-added tax (VAT)) (NICE 2015b), and with the addition of peg-IFNα plus RBV to the treatment, approximately GBP 40,000 are added to the costs (excluding VAT and monitoring costs) for a 24-week treatment course (NICE 2015a). Harvoni (ledipasvir/sofosbuvir) is the second most prescribed drug in the global market accounting for revenue of USD 9 billion **(** FiercePharma 2017)**.**

How the intervention might work

DAAs are molecules that target specific nonstructural HCV-encoded proteins and hence attempt to disrupt viral replication and infection (Pockros 2015). The effects of DAAs theoretically depend on the HCV genotype and subtype (Pockros 2015).

Why it is important to do this review

Previously published randomised clinical trials assessing the effects of DAAs have primarily focused on assessing sustained virological response as an outcome (aviraemia 24 weeks after antiviral therapy) (McHutchison 2010; Bacon 2011; Jacobson 2011; Poordad 2011; Lawitz 2013; Afdhal 2014; Wyles 2015). As examples, treatment with sofosbuvir has shown the proportion of participants with sustained virological response above 85% when combined with peg-IFNα plus RBV or RBV alone (Righi 2015); a study

assessing the use of daclatasvir in combination with peg-IFNα plus RBV in treatment-naive genotype 1 patients has shown sustained virological responses in 90% of the HCV patients (Ermis 2015); and ledipasvir in combination with sofosbuvir has, in a randomised clinical trial, shown sustained virological responses between 93% and 99% of the HCV patients (Righi 2015). Many other trials have similarly shown that DAAs seem to increase the proportion of participants with sustained virological response (McHutchison 2010; Bacon 2011; Jacobson 2011; Poordad 2011; Lawitz 2013; Afdhal 2014; Wyles 2015). Observational studies have noted associations between SVRs and increased survival and fewer liver-related complications. Such associations have been attributed to stabilisation, or even reversal, of fibrosis and attributed to the removal of the hepatitis C virus (EASL 2015). However, association cannot establish causation. As we have described in Description of the condition, a relationship between the SVR and a favourable clinical outcome has not been confirmed from randomised evidence. The clinical effects of DAAs are unclear and have been questioned (Koretz 2015). No systematic review, taking into account the risks of systematic, design, or random errors, has previously been conducted (Wetterslev 2008; Wetterslev 2009; Higgins 2011a; Jakobsen 2014a).

OBJECTIVES

To assess the benefits and harms of DAAs in people with chronic HCV.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials irrespective of publication type, publication status, and language. If, during the selection of trials, we identified any observational studies (i.e. case series; cohort studies, or quasi-randomised studies) reporting validly on adverse events of DAAs, we planned to consider these data separately, but we did not specifically search for observational studies for inclusion in this review.

Types of participants

Adults diagnosed with chronic HCV (as defined by trialists), regardless of sex, ethnicity, occupation, country of residence, and duration of infection. Both treatment-naive and treatment-experienced participants were included.

Trial participants could

1. have been treatment-naive or treatment-experienced or both;
2. have had any comorbidity to HCV, such as HIV, hepatitis B, alcoholism, and with any other specific comorbid diagnosis; and
3. have been pregnant women with chronic HCV and adults with chronic HCV who use and inject drugs.

Types of interventions

Any of the four classes of DAA drugs (Description of the intervention; Table 1).

Experimental intervention

Any of the four classes of DAA drugs administered singly, combined with another DAA, or combined with other medical co-interventions (Description of the intervention; Table 1).

Control intervention

1. No intervention or placebo.
2. Any medical intervention (except for DAAs) or any combination of medical interventions.

Types of outcome measures

Primary outcomes

1. Hepatitis C-related morbidity (diagnosed after randomisation) or all-cause mortality. Hepatitis C-related morbidity was defined as the proportion of participants with either: cirrhosis, ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy, or hepatocellular carcinoma.
2. Proportion of participants with one or more serious adverse events. We defined a serious adverse event as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, or resulted in persistent or significant disability or incapacity (ICH-GCP 1997).
3. Health-related quality of life (any valid continuous outcome scale used by the trialists).

Secondary outcomes

1. All-cause mortality.
2. Proportion of participants with ascites (as defined by trialists).
3. Proportion of participants with variceal bleeding (as defined by trialists).
4. Proportion of participants with hepato-renal syndrome (as defined by trialists).
5. Proportion of participants with hepatocellular carcinoma (as defined by trialists).
6. Proportion of participants with hepatic encephalopathy (as defined by trialists).
7. Proportion of participants with non-serious adverse events (any other adverse event not included in the definition of serious adverse events (see Primary outcomes)). We planned to assess each non-serious adverse event separately.
8. Proportion of participants without sustained virological response (as defined by trialists). Usually, this is the number of participants with detectable HCV RNA (i.e. above a lower limit of detection) in the serum by a sensitive polymerase chain reaction (PCR)-based assay or by a transcription-mediated amplification testing, 12 or 24 weeks after the end of treatment.

Exploratory outcomes

1. Proportion of participants with liver transplantation after randomisation.
2. Proportion of participants without histological improvement (as defined by trialists).
3. Proportion of participants without significant reductions in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serum levels (as defined by trialists).

We only assessed all outcomes at 'maximum follow-up'. We planned to use sensitivity analysis to assess how the different follow-up periods affected our results if we had found that the time from randomisation to maximum follow- up differed significantly between the included trials.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Controlled Trials Register (Gluud 2015), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (OvidSP), Embase (OvidSP), Science Citation Expanded (Web of Science), LILACS (Bireme), and BIOSIS (Web of Science) in order to identify relevant trials. We also searched the Chinese Biomedical Literature Database (CBM), China Network Knowledge Information (CNKI), the Chinese Science Journal Database (VIP), and the Wanfang Database. Search strategies, including the time spans of the searches, are provided in Appendix 1. Searches were last run in October 2016.

Searching other resources

We searched the bibliographic references of identified randomised clinical trials and review articles in order to find randomised clinical trials not identified by the electronic searches and handsearches. We contacted the principal authors of the identified randomised clinical trials to inquire about additional randomised clinical trials that they might know.

We also searched Google Scholar, The Turning Research into Practice (TRIP) Database, and on-line trials registries such as ClinicalTrials.gov, European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trial Registry Platform (www.who.int/ictrp), the Food and Drug Administration (FDA) (www.fda.gov), as well as pharmaceutical company sources for ongoing or unpublished trials.

Additionally, we handsearched Hepatology, New England Journal of Medicine, JAMA, BMJ, PLoS Medicine, and Annals of Internal Medicine for relevant trials.

We also searched for unpublished and grey literature trials.

Data collection and analysis

We performed the review following the recommendations of Cochrane (Higgins 2011a) and the Cochrane Hepato-Biliary Module (Gluud 2015). We performed the analyses using Review Manager 5 (RevMan 2014), STATA 14 (www.stata.com), and Trial Sequential Analysis (Thorlund 2011; TSA 2011).

Selection of studies

Fourteen review authors (EN, JF, KF, KK, GH, GP, SD, KW, MB, GB, SK, JP, DN, RK) independently and in pairs assessed all identified articles. If a trial was identified as relevant by one author, but not by another, the authors discussed the reasoning behind their decision. If they still disagreed, JCJ served as arbitrator.

Data extraction and management

Twelve review authors (EN, JF, KF, KK, GH, GP, SD, KW, MB, GB, SK, DN) independently and in pairs extracted and validated data. We used data extraction forms that were designed for the purpose. The twelve authors discussed any disagreement concerning the extracted data. If the authors still disagreed, JCJ served as arbitrator. In case of relevant data not being available, we contacted the trial authors.

Assessment of risk of bias in included studies

The review authors, working in pairs, independently assessed the risk of bias of each included trial according to the recommendations in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) and the Cochrane Hepato-Biliary Module (Gluud 2015). We used the following definitions in the assessment of risk of bias (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Higgins 2011a; Lundh 2012; Savović 2012a; Savović 2012b):

Allocation sequence generation

1. Low risk of bias: sequence generation was achieved using computer random-number generation or a random-number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
2. Unclear risk of bias: the method of sequence generation was not specified.
3. High risk of bias: the sequence generation method was not random or only quasi-randomised.

Allocation concealment

1. Low risk of bias: the allocation sequence was described as unknown to the investigators. Hence, the participants' allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit, an on-site locked computer, identical looking numbered sealed opaque envelopes, drug bottles or containers prepared by an independent pharmacist, or an independent investigator.
2. Unclear risk of bias: it was unclear if the allocation was hidden or if the block size was relatively small and fixed so that intervention allocations may have been foreseen in advance of, or during, enrolment.
3. High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and treatment providers

1. Low risk of bias: it was described that both participants and treatment providers were blinded to treatment allocation.
2. Unclear risk of bias: it was unclear whether participants and treatment providers were blinded, or the extent of blinding was insufficiently described.
3. High risk of bias: no blinding or incomplete blinding of participants and treatment providers was performed.

Blinding of outcome assessment

1. Low risk of bias: it was mentioned that outcome assessors were blinded and this was described.
2. Unclear risk of bias: it was not mentioned whether the outcome assessors were blinded, or the extent of blinding was insufficiently described.
3. High risk of bias: no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

1. Low risk of bias: missing data were unlikely to make intervention effects depart from plausible values. This could either be: 1. there were no drop-outs or withdrawals; or 2. the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar in both groups, and the trial handled missing data appropriately in an intention-to-treat analysis using proper methods (e.g. multiple imputations). Generally, the trial was judged to be at a low risk of bias due to incomplete outcome data if drop-outs were less than 5%. However, the 5% cut-off was not definitive.
2. Unclear risk of bias: there was insufficient information to assess whether missing data were likely to induce bias on the results.
3. High risk of bias: the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

Selective outcome reporting

1. Low risk of bias: a protocol was published before randomisation began and all outcome results were reported adequately.
2. Unclear risk of bias: no protocol was published.
3. High risk of bias: the outcomes in the protocol were not reported on.

Vested-interest bias

1. Low risk of bias: it was described that the trial was not sponsored by any pharmaceutical company, any person, or any group with a financial or other interest in a certain result of the trial.
2. Unclear risk of bias: it was unclear how the trial was sponsored.
3. High risk of bias: the trial was sponsored by a pharmaceutical company, a person, or a group with a certain financial or other interest in a given result of the trial.

Other bias

1. Low risk of bias: the trial appeared to be free of other bias domains that could put it at risk of bias.
2. Unclear risk of bias: the trial may or may not have been free of other domains that could put it at risk of bias.
3. High risk of bias: there were other factors in the trial that could put it at risk of bias.

Overall risk of bias

We judged trials to be at an 'overall low risk of bias' if they were assessed as 'low risk of bias' in all the above domains. We judged trials to be at an 'overall high risk of bias' if they were assessed as having unclear risk of bias or high risk of bias in one or more of the above domains.

We assessed the domains 'Blinding of outcome assessment', 'Incomplete outcome data', and 'Selective outcome reporting' for each outcome result. Thus, we assessed the bias risk for each outcome result in addition to the overall bias risk for each trial.

Measures of treatment effect

Dichotomous outcomes

We planned to present risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes. However, since we found several trials with zero events, we handled this according to Sweeting 2004, and used odds ratios (OR) instead.

Continuous outcomes

We included both follow-up scores and change scores in the analyses. We used follow-up scores in the analyses in the case when both were reported. We presented the mean differences (MD) and the standardised mean differences (SMD) with 95% CI for continuous outcomes.

Unit of analysis issues

For cross-over trials, we only included participants from the first treatment period in the trial. We avoided counting data more than once from participants in control arms of trials with multiple experimental intervention arms by dividing the sample size and number of participants experiencing the event by the number of eligible treatment arms used.. There were no other unit of analysis issues.

Dealing with missing data

Dichotomous outcomes

If the trialists used proper methodology (e.g. multiple imputation) to deal with missing data, we used these data in our primary analysis. We did not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses (see below), we imputed missing data (Jakobsen 2014a).

Continuous outcomes

If trialists used proper methodology (e.g. multiple imputation) to deal with missing data, we used these data in our primary analysis (Jakobsen 2014a). We primarily used follow-up scores. If only change-from-baseline values were reported, we analysed change scores together with follow-up scores (Higgins 2011c). If standard deviations (SDs) were not reported, we calculated these using data from the trial if possible. We did not impute missing values for any outcomes in our primary analysis (Jakobsen 2014a).

Sensitivity analyses

To assess the potential impact of the missing data for dichotomous outcomes, we performed the two following sensitivity analyses (Jakobsen 2014a).

1. 'Best-worst-case' scenario: we assumed that all participants lost to follow-up in the experimental group had survived, had no serious adverse event, and had no morbidity (for all dichotomous outcomes); and all those participants with missing outcomes in the control group had not survived, had a serious adverse event, and had morbidity (for all dichotomous outcomes).
2. 'Worst-best-case' scenario: we assumed that all participants lost to follow-up in the experimental group had not survived, had a serious adverse event, and had morbidity (for all dichotomous outcomes); and that all those participants lost to follow-up in the control group had survived, had no serious adverse event, and had no morbidity (for all dichotomous outcomes).

Assessment of heterogeneity

We primarily inspected forest plots visually in order to assess if there were signs of statistical heterogeneity (Jakobsen 2014a). We also assessed the presence of statistical heterogeneity using the Chi^2 test with significance set at P value < 0.10 and measured the quantities of heterogeneity using the I^2 statistic (Higgins 2003; Deeks 2011).

Assessment of reporting biases

We primarily inspected funnel plots visually in order to assess if there were signs of reporting bias if 10 or more trials were included (Jakobsen 2014a). Using the asymmetry of the funnel plot, we assessed the risk of bias. For dichotomous outcomes we also assessed if there were signs of asymmetry with the Harbord test if τ^2 was less than 0.1 and with the Rücker test if τ^2 was more than 0.1 (Harbord 2006; Sterne 2011). For continuous outcomes we used the regression asymmetry test (Egger 1997).

Data synthesis

We based our primary conclusions on the results of the primary outcomes with low risk of bias. Our primary analyses were based on trials assessing the effects of DAAs on the market and trials using similar medical co-interventions in both the experimental and control group.

Meta-analysis

We undertook this meta-analysis according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We used the statistical software Review Manager 5 provided by Cochrane to analyse data (RevMan 2014). When we observed unbalanced data, a large number of zero events, and rare incidences of events in the control group, we excluded trial results with zero events in both groups (Deeks 2011). We then used reciprocal zero cell correction and fixed meta-analysis in STATA 14 (www.stata.com) and the following subgroup analyses were based on the inverse variance method (Sweeting 2004; Deeks 2011).

Assessment of significance

We assessed our intervention effects with both random-effects meta-analysis and fixed-effect meta-analysis (Jakobsen 2014a). We used the more conservative point estimate of the two (Jakobsen 2014a). The more conservative point estimate was the estimate closest to zero effect. If the two estimates were equal, we used the estimate with the widest CI. Our analyses showed that multiple trials had zero and rare events. In these cases we used fixed-effect meta-analysis (Sweeting 2004). We assessed three primary outcomes; therefore, we considered a P value of 0.025 or less as statistically significant on the primary outcomes (Jakobsen 2014a; Jakobsen 2014b; Jakobsen 2016a). We assessed eight secondary outcomes; therefore, we considered a P value of 0.011 or less as statistically significant on the secondary outcomes (Jakobsen 2014a; Jakobsen 2014b; Jakobsen 2016a). We used an eight-step procedure to assess if the thresholds for statistical significance and clinical significance were crossed (Jakobsen 2014a).

Trial Sequential Analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. Therefore, we performed Trial Sequential Analysis (Wetterslev 2008; Wetterslev 2009; Brok 2010; Jakobsen 2014a) on the outcomes in order to calculate the required information size and assessed the eventual breach of the cumulative Z-curve of the relevant trial sequential monitoring boundaries for benefit, harm, or futility (Wetterslev 2008; Wetterslev 2009; Brok 2010; Jakobsen 2014a). Thereby, we wished to control the risks of type I errors and type II errors. A more detailed description of Trial Sequential Analysis can be found at www.ctu.dk/tsa (Thorlund 2011; TSA 2011).

For dichotomous outcomes, we estimated the required information size based on the proportion of participants with an outcome in the control group, a relative risk reduction of 20%, an alpha of 2.5% and 1.1% depending on primary or secondary outcome, a beta of 20%, and the observed diversity in the trials in the meta-analysis (Jakobsen 2014a). For continuous outcomes, we estimated the required information size based on the SD observed in the control group of trials with low risk of bias, a minimal relevant difference of 50% of this observed SD, an alpha of 2.5% and 1.1% depending on primary or secondary outcome, a beta of 20%, and the observed diversity in the trials in the meta-analysis (Jakobsen 2014a).

'Summary of findings' table

We created 'Summary of findings' tables on three of our outcomes (all-cause mortality, serious adverse events, and no sustained virological response) using GRADEpro Guideline Development Tool (www.gradepro.org). We chose these three outcomes because we consider these outcomes to be the important outcomes for decision makers; all-cause mortality and serious adverse events because of the obvious clinical relevance of these outcomes, and no sustained virological because of the focus on this surrogate outcome in hepatitis C intervention research (see Description of the condition and Agreements and disagreements with other studies or reviews). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias, indirectness of the evidence, heterogeneity of the data, imprecision of effect estimates (wide CIs) (Jakobsen 2014), and risk of publication bias (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013).

Subgroup analysis and investigation of heterogeneity

We planned a large number of subgroup analyses (see below). We did not specify in detail how exactly we would compare the subgroups, but we chose to use the formal test for subgroup difference (Deeks 2011) to assess if there was evidence of a difference between subgroups. and if the formal test for subgroup differences (Deeks 2011) showed evidence of a difference then we assessed each subgroup separately and reported each subgroup meta-analysis result. We chose to use the formal test for subgroup difference (Deeks 2011) to limit the number of comparisons and hence problems with multiplicity. The large number of comparisons increases the risks of type I errors and type II errors (Jakobsen 2014a; Jakobsen 2016a).

1. Trials with overall low risk of bias compared to trials with overall high risk of bias.

2. Trials randomising HCV participants following the different combinations of DAAs assessed.
3. Trials randomising HCV participants with and without HIV infection.
4. Trials randomising HCV participants with and without HIV infection, hepatitis B, alcoholism, severe fibrosis, cirrhosis, mixed group, or any other specific comorbid diagnosis.
5. Trials randomising HCV participants specifically according to the different HCV genotypes (both comparing the effects of different drug combination on the same genotype and the effects each specific drug combination on each genotype).
6. Trials randomising HCV participants specifically according to the different IL28 genotypes (both comparing the effects of different drug combination on the same IL 28 genotype and the effects each specific drug combination on each IL28 genotype).
7. Trials randomising HCV participants from Asian compared to non-Asian regions (Thomas 2009).
8. Trials randomising HCV participants according to specific races or ethnicities (Thomas 2009).
9. Trials that are stopped early (not reaching the planned sample size) compared to trials that are not stopped early.
10. Trials randomising treatment-naive participants compared to previously-treated patients.
11. Trials assessing the effects of DAAs combined with IFN compared to trials assessing the effects of DAAs combined with no IFN.
12. Trials assessing the effects of DAAs combined with RBV compared to trials assessing the effects of DAAs combined with no RBV.
13. Trials randomising HCV participants with and without chronic kidney disease (as defined by trialists).
14. Trials randomising HCV participants with and without mixed cryoglobulinaemia (as defined by trialists).

Sensitivity analysis

Please see above under Dealing with missing data. Furthermore, we intended to use sensitivity analyses whenever we wanted to assess robustness of our findings (Jakobsen 2014a).

RESULTS

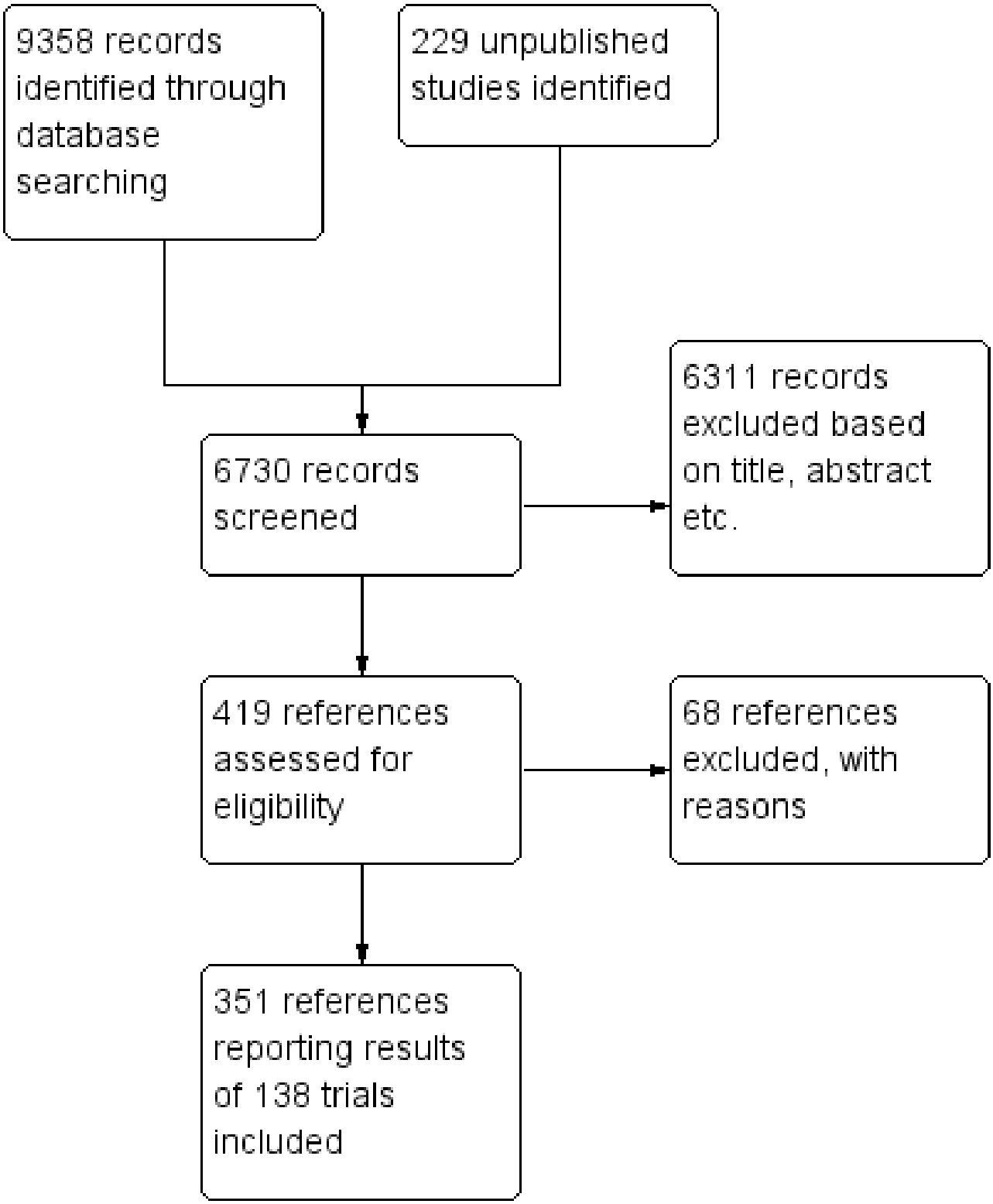
Description of studies

We assessed all trials according to the *Cochrane Handbook of Systematic Reviews of Interventions* (Schünemann 2011), and the protocol for this review Jakobsen 2016b. Characteristics of each trial can be found in Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies.

Results of the search

We identified a total of 9358 potentially relevant references through searching the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Science Citation Expanded, LILACS, BIOSIS, Chinese Biomedical Literature Database (CBM), China Network Knowledge Information (CNKI), the Chinese Science Journal Database (VIP), and the Wanfang Database. Additionally, 229 unpublished records were identified through United States Food and Drug Administration, clinical trials registers of the USA and Europe, and company websites. We excluded 2857 reference duplicates. Accordingly, 6730 were screened, and 6312 records were excluded based on titles and abstracts. We assessed 419 published/unpublished full-text papers for eligibility. Of these we excluded 68 references because of the inclusion criteria and exclusion criteria. Reasons for exclusion are listed in the Characteristics of excluded studies table. We included 351 references reporting results of 138 trials. Additionally two trials were ongoing trials. The study flow chart can be seen in Figure 2 (Moher 2009).

Figure 2. Study flow diagram



Included studies

We included 351 references on 138 trials (Figure 2). The trials were conducted between 2004 and 2016. Only 85 of these trials assessed DAAs on the market or under development. Fifty-seven trials were on withdrawn DAAs. The trials were from 34 different countries located in six continents: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, Denmark, France, Germany, India, Ireland, Israel, Italy, Japan, Korea, Lithuania, Mexico, Moldova, Netherlands, New Zealand, Poland, Puerto Rico, Romania, Russia, South Korea, Spain, Sweden, Taiwan, Thailand,

UK, USA. For further details on included studies see Characteristics of included studies.

Participants

A total of 25,232 participants were randomised in 138 trials (two trials did not report the number of randomised participants). A total of 13,466 participants were randomised in the 84 trials assessing DAAs on the market or under development. The number of participants in each trial ranged from 10 to 1097 (average 182 participants).

We included 17 trials where the participants were treatment-experienced, 95 trials where the participants were treatment-naive, 24 trials where the participants were mixed (both treatment-naive and treatment-experienced), and five trials where it was unclear whether the participants were treatment-experienced or treatment-naive.

We included participants with different HCV genotypes: HCV genotype 1 (119 trials), HCV genotype 2 (eight trials), HCV genotype 3 (six trials), HCV genotype 4 (nine trials), and HCV genotype 6 (one trial). Twelve trials did not specify which HCV genotypes they assessed.

We included three trials where HIV was an inclusion criteria, 102 where HIV was an exclusion criteria, one trial with both HIV and non-HIV participants, and 35 trials where it was unclear if HIV was an inclusion/exclusion criteria.

Two trials included only participants with diagnosed cirrhosis, 44 trials included both participants with and without cirrhosis, 67 trials did not include participants with cirrhosis or advanced liver disease, and in 25 trials it was unclear wether participants with cirrhosis or advanced liver disease were included.

Experimental interventions

Eighty-four trials were on DAAs on the market or under development. Fifty-seven trials were on withdrawn (or discontinued) DAAs. The intervention period ranged from one day to 48 weeks with an average of 14 weeks. The follow-up in the included trials ranged from one day to 120 weeks with an average of 34 weeks. The 138 trials used 51 different DAAs: ACH-2064 (n = 1); alisporivir (n = 1); ALS-2200 (n = 1); asunaprevir (n = 3); balapiravir (n = 2); beclabuvir (n = 2); BILB-1941 (n = 1); BILN-2061 (n = 1); BIT-25 (n = 1); boceprevir (n = 12); ciluprevir (n = 2); daclatasvir (n = 6); danoprevir (n = 5); deleobuvir (n = 2); faldaprevir (n = 8); filibuvir (n = 2); grazoprevir (n = 2); GS-6620 (n = 1); GS-9256 (n = 2); GS-9451 (n = 2); GS-9669 (n = 1); GS-9851 (n = 1); GS-9857 (n = 1); GSK2336805 (n = 2); GSK2878175 (n = 1); HCV-796 (n = 1); IDX-184 (n = 2); INX-09189 (n = 1); ledispasvir (n = 1); mericitabine (n = 6); mixed (n = 13); narlaprevir (n = 2); nesbuvir (n = 2); odalasavir (n = 1); ombitasvir (n = 1); paritaprevir (n = 1); PHX1766 (n = 1); PPI-461 (n = 1); PSI-352938 (n = 1); samatasvir (n = 1); setrobuvir (n = 2); simeprevir (n = 11); sofosbuvir (n = 6); sovaprevir (n = 2); tegobuvir (n = 2); telaprevir (n = 10); valopicitabine (n = 1); vaniprevir (n = 5); VCH-759 (n = 1); VCH-916 (n = 1); velpatasvir (n = 1); VX-222 (n = 1).

Control interventions and co-interventions

We included 128 trials where the control group received a matching placebo and 13 trials where the control group did not receive placebo. We included 46 trials where neither intervention group (DAA and control) received RBV nor IFN; 79 trials where both groups received RBV and IFN; two trials where both groups received IFN and no RBV; five trials where both groups received RBV and no IFN; three trials where only the control group received IFN and RBV; two trials where only the control group received RBV; and one trial where only the experimental group received RBV and IFN. We included three trials where an additional DAA (different from the experimental type of DAA) was given as co-intervention in both the experimental and control group.

Funding

One trial was not funded by someone with a financial interest in a certain result of the trial (Mostafa 2015). In the remaining 140 trials it was either not reported, in sufficient detail, how the trial was funded or the trial was financially supported by someone with a financial interest in a certain result of the trial (Figure 1).

Excluded studies

We excluded 68 studies. Of these, 38 studies had a control group receiving an intervention beyond our inclusion and exclusion criteria (33 studies had DAA as control intervention, five studies had no control group); seven studies did not use DAA as intervention; 12 studies were not randomised; seven studies were comments; and four studies used healthy participants. Characteristics of excluded studies table presents a summary of the reasons for the exclusions.

Risk of bias in included studies

Allocation

We assessed the generation of the allocation sequence generation as low risk of bias in 37/138 trials. The remaining trials were described as being randomised but they did not describe the method used for allocation sequence generation in sufficient detail, resulting in an 'uncertain risk of bias' (Figure 1).

We assessed the methodology used for allocation concealment as low risk of bias in 38/138 trials. The methodology used for allocation concealment was unclear or we assessed it as high risk of bias in the remaining trials (Figure 1).

Blinding

We assessed the blinding of participants and personnel as low risk of bias in 28/138 trials. The remaining trials either did not describe the blinding of participants and personnel in sufficient detail (unclear) or we assessed the methodology as high risk of bias (Figure 1).

We assessed the blinding of outcome assessors as low risk of bias in 14/138 trials. The methods for blinding of outcome assessors for the remaining trials were either not described in sufficient detail (unclear) or we assessed them as high risk of bias (Figure 1).

Incomplete outcome data

We assessed trials' handling of incomplete outcome data as low risk of bias in 49/138 trials. The remaining trials either did not describe how they handled incomplete outcome data (unclear) or we assessed the methodology as high risk of bias (Figure 1).

Selective reporting

We assessed selective outcome reporting as low risk of bias in 49/138 trials. The remaining trials either did not register or publish a protocol with predefined outcomes before the randomisation

began or the methodology was assessed as high risk of bias (Figure 1).

Other potential sources of bias

We assessed the vested-interest domain as low risk of bias in one trial (Mostafa 2015) and high risk of bias in the remaining 140 trials; either because the funding or financial interests were not reported in sufficient detail or because the trial was financially supported by someone with a financial interest in a certain result of the trial.

Overall risk of bias

Based on our predefined 'Risk of bias' assessment, we considered all 138 trials at high risk of bias. Many trials were judged to have unclear risk of bias in several domains, and additional information could not be obtained from the trial authors. Only four trials had low risk of bias in 7/8 domains (Wedemeyer 2013; Feld 2014; Zeuzem 2014a; C-EDGE TN 2015. The latter four trials were at high risk of bias in the vested-interest bias risk domain (Figure 1). Additional information can be found in the 'Risk of bias' summary (Figure 1).

Effects of interventions

See: **Summary of findings for the main comparison** Direct-acting antivirals versus control; **Summary of findings 2** Direct-acting antivirals withdrawn from the market versus control

Analyses of trials assessing the effects of DAAs on the market or under development

Hepatitis C-related morbidity or all-cause mortality

When analysing the composite outcome hepatitis C-related morbidity or all-cause mortality, all events were deaths only.

Meta-analysis

Eleven trials with a total of 2996 participants provided useful data on all-cause mortality. A total of 15/2377 (0.63%) participants died in the DAA groups versus 1/617 (0.16%) participants who died in the control groups during the observation period. Because of the unbalanced data, the large number of zero events, and the rare incidence of events in the control group, we used reciprocal zero cell correction and fixed-effect meta-analysis (STATA 14; www.stata.com) (Sweeting 2004). The extracted data can be found in the standard results section, but the meta-analysis results can be found in the STATA forest plots. Meta-analysis showed no evidence of a difference when assessing risk of all-cause mortality (OR 3.72, 95% CI 0.53 to 26.18, P = 0.19; I^2 = 0%, 11 trials, very low-quality evidence, Analysis 1.1).

Heterogeneity

Neither visual inspection of the forest plots nor tests for statistical heterogeneity (I^2 = 0%, P = 0.99) indicated significant heterogeneity.

Risk of bias and sensitivity analyses

The risk of bias of this outcome result was assessed as high risk of bias.

Additional analyses

Due to the total lack of data on hepatitis C-related morbidity and the low number of events on all-cause mortality, we did not perform additional analysis including Trial Sequential Analysis, Bayes factor, funnel plots, or subgroup analysis.

Serious adverse events

Meta-analysis

Forty-three trials with a total of 15,817 participants reported results on serious adverse events. A total of 376/13,574 (2.77%) participants in the DAA groups had one or more serious adverse events versus a total of 125/2243 (5.57%) participants in the control groups during the observation period (Table 2). Because of the unbalanced data, the large number of zero events, and the rare incidence of events in the control groups, we used reciprocal zero cell correction and fixed-effect meta-analysis (STATA 14; www.stata.com) (Sweeting 2004; Deeks 2011). The extracted data can be found in the Data and analyses section, but the meta-analysis is performed in STATA (figure not shown). The meta-analysis showed no evidence of a difference between the two intervention groups (OR 0.93, 95% CI 0.75 to 1.15, P = 0.52, I^2 = 0%; 43 trials, very low-quality evidence, Analysis 2.1).

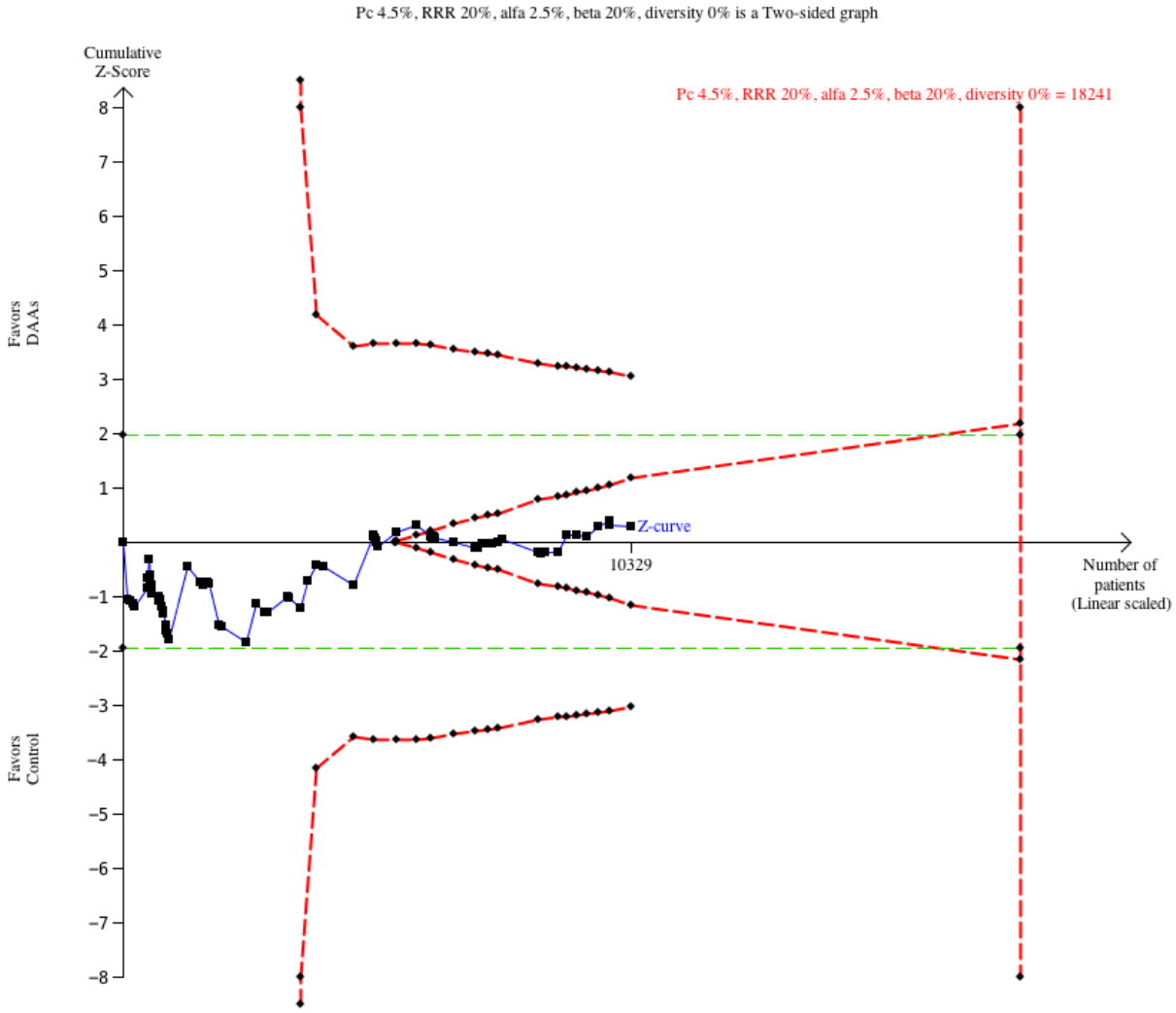
Heterogeneity

Neither visual inspection of the funnel plots nor tests for statistical heterogeneity (I^2 = 0%, P = 0.99) indicated significant heterogeneity.

Trial Sequential Analysis

The Trial Sequential Analysis showed that the Z-curve crossed the trial sequential monitoring boundary for futility. Hence, there is firm evidence that DAAs versus control do not reduce the risk of serious adverse events by 20% or more (Figure 3).

Figure 3. Trial Sequential Analysis of the effects of direct-acting antivirals on the market or under development versus placebo or no intervention on risk of serious adverse events. The analysis was based on a proportion in the control group (Pc) of 4.5%, a relative risk reduction (RRR) of 20%, and alfa of 2.5%, a beta of 20%, and a diversity of 0%. The cumulative Z-curve enters the futility area after the randomisation of about 6000 participants.



Bayes factor

Bayes factor was calculated based on a RR of 20%, and the meta-analysis result (OR 0.93). Bayes factor was 2.41 which is above the Bayes factor threshold for significance of 0.1, supporting that there seems to be more evidence for the null hypothesis compared to the evidence for an intervention effect of 20% relative risk reduction (RRR).

Risk of bias and sensitivity analyses

The risk of bias of the outcome result was assessed as high risk of bias.

The best-worst case meta-analysis (OR 0.79, 95% CI 0.64 to 0.97, I^2= 0%, P = 0.022) (see Dealing with missing data) and worst-best case meta-analysis (OR 1.06, 95% CI 0.86 to 1.31, I^2 = 0%, P = 0.56) (see Dealing with missing data) showed that incomplete outcome data may influence the results.

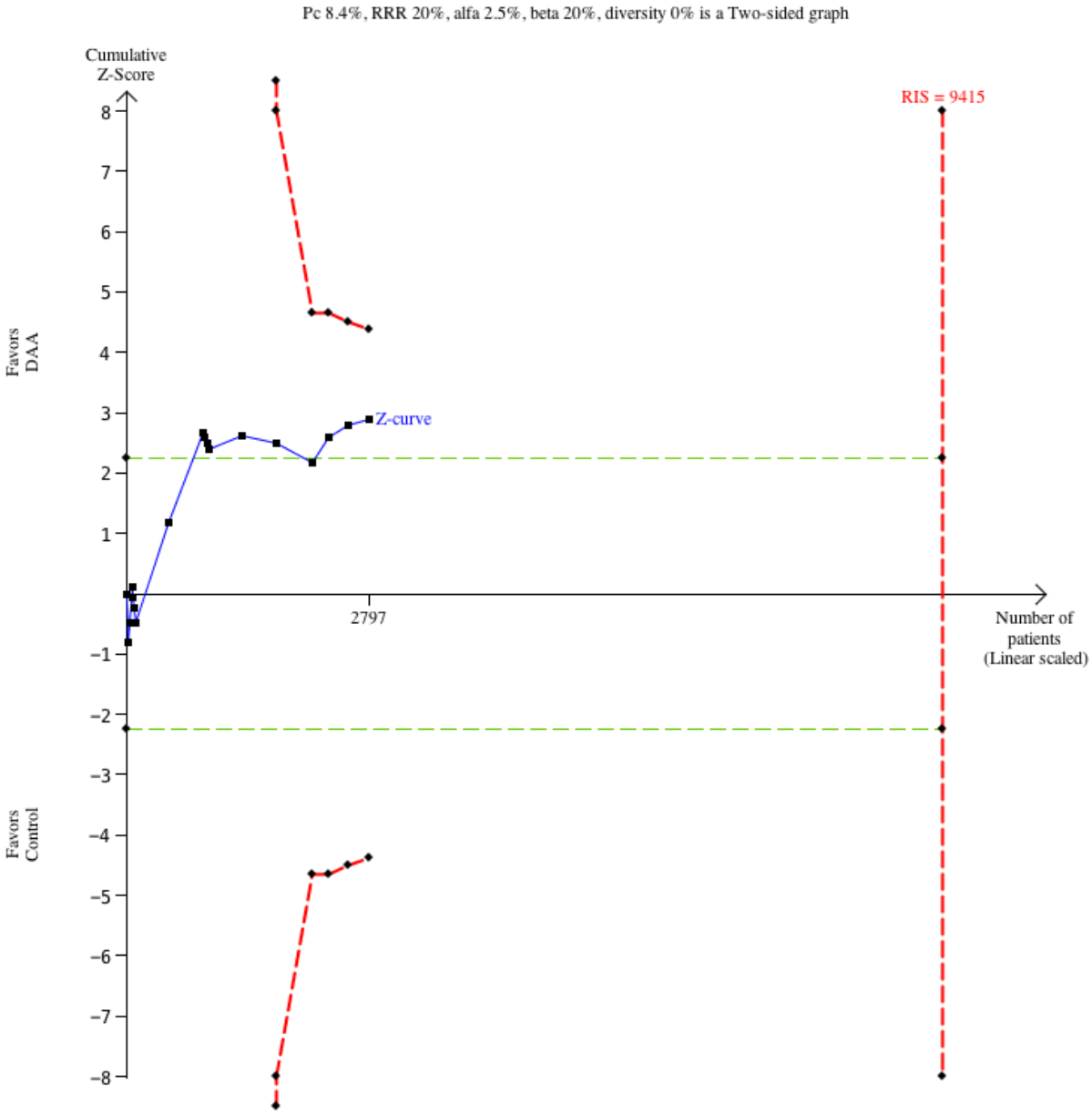
Visual inspection of the funnel plots showed no clear signs of asymmetry.

Subgroup analyses

The test for subgroup differences comparing the effects of each type of DAA showed no evidence of a difference (P = 0.49). The only single DAA that showed evidence of a difference when meta-analysed separately was simeprevir (OR 0.62, 95% CI 0.45 to 0.86, P = 0.004; Analysis 2.3). However, a post hoc Trial Sequential Analysis showed that the trial sequential monitoring boundary for benefit was not crossed (Figure 4). Furthermore, if just one trial with an extreme result (Forns 2014) was excluded from the analysis then a post hoc sensitivity meta-analysis did not show evidence of a difference (OR 0.70, 95% CI 0.49 to 1.01, P = 0.053). The remaining P values for each DAA meta-analysed separately were: paritaprevir P = 0.69; asunaprevir P = 0.20; alisporivir P = 0.15; daclatasvir P = 0.75; danoprevir P = 0.15; mericitabine P = 0.96; GSK2336805 P = 0.63;

sofosbuvir P = 0.66; GS-9451 P = 0.70; vaniprevir P = 0.06; GS-9851 P = 0.83; beclabuvir P = 0.44 (Analysis 2.3).

Figure 4. Trial Sequential Analysis of the effects of simeprevir versus placebo or no intervention on risk of serious adverse events. The analysis was based on a proportion in the control group (Pc) of 8.4%, a relative risk reduction (RRR) of 20%, and alfa of 2.5%, a beta of 20%, and a diversity of 0%. The cumulative Z-curve crosses the naive type I error level of 5%, but it does not cross the trial monitoring boundary for benefit.



The test for subgroup differences showed no evidence of a difference in five subgroup analyses (treatment-naive compared to treatment-experienced, P = 0.39; IFN in both groups compared to no IFN in both groups, P = 0.277; RBV in both groups compared to no RBV in both groups, P = 0.10; viral genotype 1 compared to mixed, P = 0.09); subclasses of DAAs (P = 0.31). Because of no relevant data it was not possible to conduct any of the remaining planned subgroup analyses (Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9; Analysis 2.10; Analysis 2.11; Analysis 2.12; Analysis 2.13; Analysis 2.14; Analysis 2.15; Analysis 2.16; Analysis 2.17).

As a post hoc analysis we calculated the median dose of each assessed DAA. We then divided all trials reporting relevant data into two groups: 1. trials assessing the effects of a DAA over or at the median dose, and 2. trials assessing the effects of a DAA below the median dose. The test for subgroup differences showed no evidence of a difference (P = 0.67).

Assessment of clinical significance

We did not assess the clinical significance of the results on serious adverse events because the threshold for statistical significance was not crossed.

Health-related quality of life

Only one trial assessed the effects of a DAA (sofosbuvir, DAA on the market) on quality of life (SF 36 mental score and SF 36 physical score) (FISSION 2013). There was no evidence of a difference between the DAA and control on either SF 36 mental score or SF 36 physical score (FISSION 2013). An additional trial also assessed the effects sofosbuvir on quality of life (SF 36 mental score and SF 36 physical score) (POSITRON 2013). However, this trial randomised participants to a combination of DAAs and RBV versus placebo. There was no evidence of a difference between the compared groups on either SF 36 mental score or SF 36 physical score (POSITRON 2013).

No sustained virological response

Meta-analysis

Thirty-two trials with a total of 7115 participants reported results on no sustained virological response. A total of 1214/5347 (22.7%) in the DAA groups and a total of 955/1768 (54.0%) participants in the control group had no sustained virological response during the observation period. Meta-analysis showed that DAAs seemed to decrease the risk of no sustained virological response (RR 0.44, 95% CI 0.37 to 0.52, P < 0.00001, I^2 = 77%, 32 trials, low-quality evidence; Analysis 3.1).

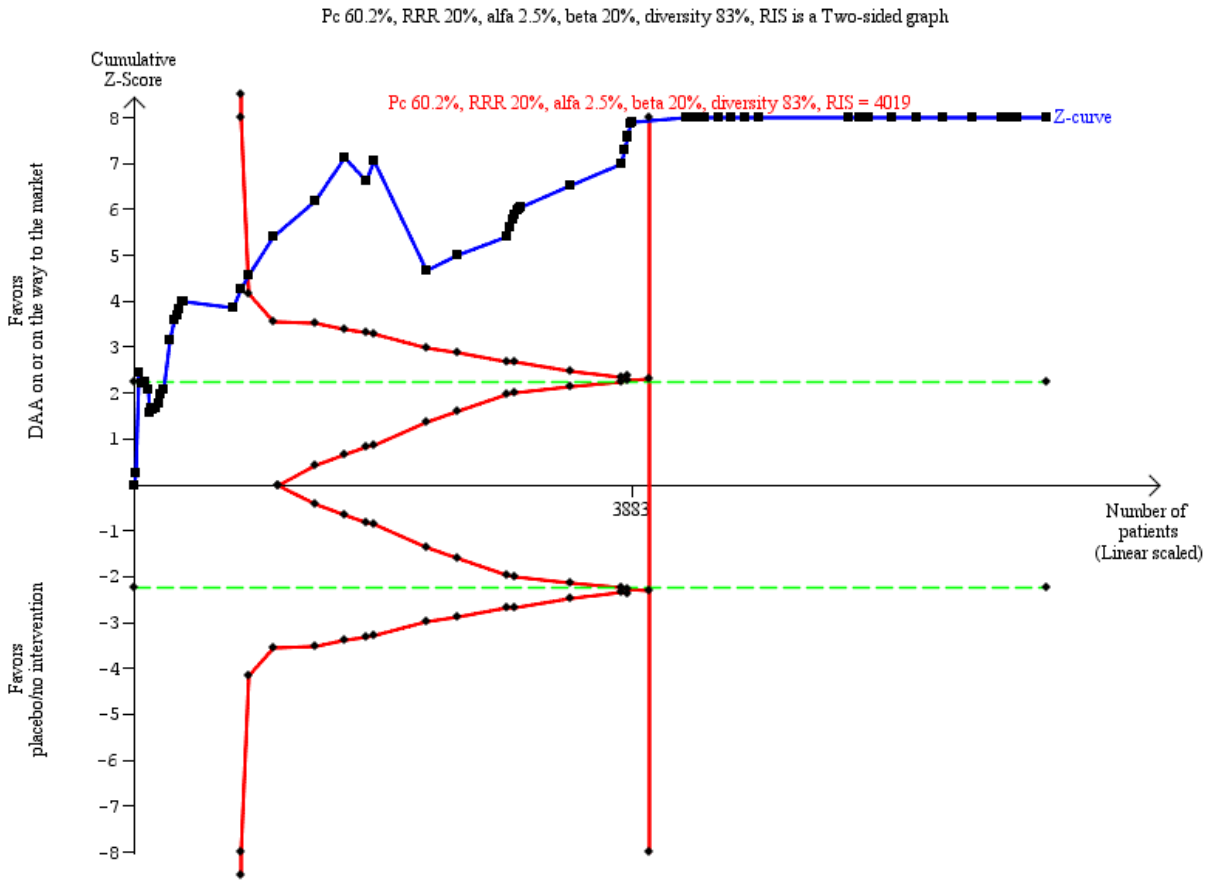
Heterogeneity

Visual inspection of the funnel plots did not indicate significant statistical heterogeneity (Analysis 3.1). The tests for statistical heterogeneity (I^2 = 78%; P < 0.00001) indicated significant heterogeneity.

Trial Sequential Analysis

The Trial Sequential Analysis showed that the Z-curve crossed the trial sequential monitoring boundary for benefit. Hence, there is evidence that DAAs versus control do reduce the risk of no sustained virological response by 20% or more (Figure 5).

Figure 5. Trial Sequential Analysis of the effects of direct-acting antivirals on the market or under development versus placebo or no intervention on risk of no sustained virological response. The analysis was based on a proportion in the control group (Pc) of 60.2%, a RRR of 20%, and alfa of 2.5%, a beta of 20%, and a diversity of 83%. After randomisation of about 1000 participants, the cumulative Z-curve crosses the trial sequential monitoring boundary for benefit.



Bayes factor

Bayes factor was calculated based on a RR of 20%, and the meta-analysis result (OR 0.44). Bayes factor of 3.29 * 10^{-25} was below the Bayes factor threshold for significance of 0.1, supporting that there seems to be more evidence for a 20 % RRR on risk of no sustained virological response compared to evidence for the null hypothesis.

Risk of bias and sensitivity analyses

The risk of bias of the outcome result was assessed as high.

The best-worst (OR 0.41, 95% CI 0.34 to 0.49, Analysis 3.18) and the worst-best (OR 0.51, 95% CI 0.43 to 0.60, Analysis 3.19) case meta-analyses showed that incomplete outcome data bias did not seem to have any potential impact on the meta-analysis result.

Visual inspection of the funnel plots showed signs of asymmetry. However, the Harbord test showed no evidence of a difference (P = 0.52).

Subgroup analyses

Types of DAA

The test for subgroup differences comparing the effects of each type of DAA showed evidence of a difference between the different DAAs (P < 0.001, I^2 = 61.1%, Analysis 3.3). When analysed separately, the following single DAAs all showed evidence of an effect when assessing no sustained virological response: asunaprevir (RR 0.49, 95% CI 0.29 to 0.85, Analysis 3.3); daclatasvir (RR 0.60, 95% CI 0.50 to 0.73, Analysis 3.3); danoprevir (RR 0.38, 95% CI 0.28 to 0.51, Analysis 3.3); GS-9451 (RR 0.42, 95% CI 0.26 to 0.67, Analysis 3.3); simeprevir (RR 0.39, 95% CI 0.33 to 0.46, Analysis 3.3); sofosbuvir (RR 0.34, 95% CI 0.20 to 0.58, Analysis 3.3); and vaniprevir (RR 0.33, 95% CI 0.25 to 0.43, Analysis 3.3).

Subclass of DAA

The test for subgroup differences comparing the effects of each type of DAA showed evidence of a difference between the different DAAs (P < 0.00001, I^2 = 95%, Analysis 3.4). When analysed separately, the following subclasses of DAAs all showed evidence of an effect when assessing no sustained virological response: NS3/NS4A inhibitors (RR 0.41, 95% CI 0.36 to 0.46, Analysis 3.4); NS5B inhibitors (NPI) (RR

0.57, 95% CI 0.36 to 0.90); and NS5A inhibitors (RR 0.59, 95% CI 0.49 to 0.69, Analysis 3.4).

Viral genotype

The test for subgroup differences comparing the effects of DAAs in different genotypes showed evidence of a difference between the subgroups (P = 0.002; I^2 = 73.6%, Analysis 3.7). Only trials randomising participants with HCV genotype 1 (RR 0.43, 95% CI 0.37 to 0.50, Analysis 3.7) and HCV genotype 4 (RR 0.10, 95% CI 0.02 to 0.68, Analysis 3.7) showed an evidence of a difference when analysed separately.

Human genotype

The test for subgroup differences comparing the effects of DAAs in different human genotypes did not show evidence of a difference between the subgroups (P = 0.62; I^2 = 0%, Analysis 3.8). All of the subgroups showed clear evidence of differences in favour of DAAs when analysed separately (Analysis 3.8).

Trials conducted in an Asian region compared to trials not conducted in an Asian region

The test for subgroup differences comparing the effects of DAAs in trials conducted in an Asian region compared to trials conducted outside an Asian region showed evidence of a difference between the subgroups, with larger effects in Asia: (P < 0.02, I^2 = 70.3%, Analysis 3.9). When analysed separately, both trials randomising Asian (RR 0.34, 95% CI 0.28 to 0.42) and non-Asian (RR 0.51, 95% CI 0.43 to 0.60) participants showed clear evidence of differences in favour of DAAs (Analysis 3.9).

Treatment-experienced compared to treatment-naive

The test for subgroup differences comparing the effects of DAAs in trials randomising treatment-experienced participants to trials randomising treatment-naive participants, did not show evidence of a difference between the subgroups (P = 0.46; I^2 = 0%, Analysis 3.12). When analysed separately, both trials randomising treatment-experienced (RR 0.50, 95% CI 0.36 to 0.69) and treatment-naive (RR 0.48, 95% CI 0.41 to 0.56) participants showed clear evidence of differences in favour of DAAs (Analysis 3.12).

IFN as co-intervention compared to no IFN as co-intervention

The test for subgroup differences comparing the effects of DAAs in trials using IFN as co-intervention in both groups compared to trials not using IFN as co-intervention in both groups, did not show evidence of a difference between the subgroups (P = 0.68, I^2 = 0%, Analysis 3.13).

None of the remaining planned subgroup analyses were possible to conduct because of the lack of relevant trial data.

As a post hoc analysis we calculated the median dose of each assessed DAA. We then divided all trials reporting relevant data into two groups: 1. trials assessing the effects of a DAA over or at the median dose, and 2. trials assessing the effects of a DAA below the median dose. The test for subgroup differences showed no evidence of a difference (P = 0.56; Analysis 3.20).

Assessment of clinical significance

A number of the analyses showed clear evidence of an effect. However, the clinical relevance of these effects on a non-validated surrogate outcome results is unclear (see Background).

Analysis of trials using RBV and IFN only in the control group

Analysis of trials using RBV and IFN only in the control group and not as co-intervention in the experimental group, showed that there was no evidence of a difference between the DAAs versus RBV and IFN on risk of serious adverse events (OR 1.81, 95% CI 0.74 to 4.44, P = 0.192, I^2 = 0%, 3 trials, very low-quality evidence).

Our results are summarised in our 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2).

Analyses of trials assessing the effects of withdrawn DAAs

Hepatitis C-related morbidity or all-cause mortality

When analysing the composite outcome hepatitis C-related morbidity or all-cause mortality, all events were deaths only.

Meta-analysis showed no evidence of an effect when assessing the effects of withdrawn DAAs on hepatitis C-related morbidity or all-cause mortality (OR 0.64, 95% CI 0.23 to 1.79, P = 0.40, I^2 = 0%; 5 trials, very low-quality evidence). Test for subgroup differences between DAAs on the market and withdrawn DAAs showed no evidence of a difference (P=0.45) (Analysis 5.1)

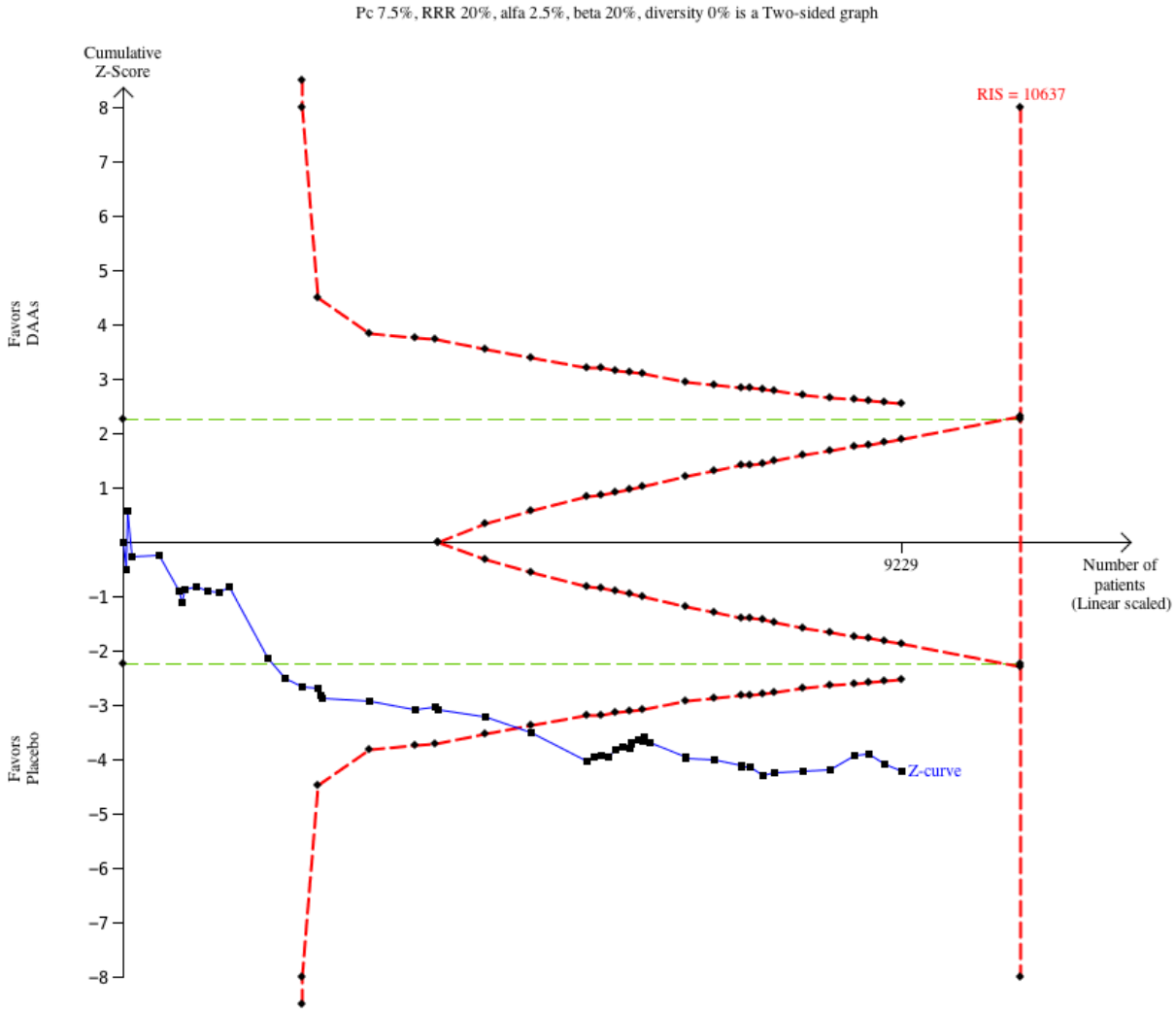
Additional analyses

Due to the total lack of data on hepatitis C-related morbidity and the low number of events on all-cause mortality, we did not perform additional analysis, including Trial Sequential Analysis, Bayes factor, funnel plots, or subgroup analysis.

Serious adverse events

Meta-analysis showed that withdrawn DAAs seemed to increase the risk of serious adverse events (OR 1.45, 95% CI 1.22 to 1.73, P = 0.001, I^2 = 0%, 29 trials, very low-quality evidence). A post hoc Trial Sequential Analysis confirmed this meta-analysis result (Figure 6). Test for subgroup differences between DAAs on the market and withdrawn DAAs showed evidence of a difference between the DAAs that are on the market and the withdrawn DAAs (P < 0.001) (Analysis 6.1).

Figure 6. Trial Sequential Analysis of the effects of withdrawn direct-acting antivirals versus placebo or no intervention on risk of serious adverse events. The analysis was based on a proportion in the control group (Pc) of 7.5%, a RRR of 20%, and alfa of 2.5%, a beta of 20%, and a diversity of 0%. After randomisation of about 5000 participants, the cumulative Z-curve crosses the trial sequential monitoring boundary for harm.



No sustained virological response

Meta-analysis of trials assessing the effects of withdrawn DAAs showed similar results to the meta-analysis of trials assessing the effects of DAAs on the market or under development when assessing no sustained virological response (Analysis 7.1).

Without significant reductions in serum ALT or AST

Four trials reported results on participants without significant reductions in serum ALT or AST, but all of these trials assessed the effects of withdrawn DAAs (Analysis 12.1). Meta-analysis showed that these withdrawn DAAs seemed to decrease the risk of no significant reduction of serum ALT or AST (RR 0.79, 95% CI 0.68 to 0.92, Analysis 12.1).

Non-serious adverse events

A large number of non-serious adverse events were reported in the included trials. Overall, 92.4% of the DAA participants experienced one or more non-serious adverse event compared to 91.5% control participants. We have summarised these in Table 3. We plan to analyse each of these adverse events separately, in detail, in a later publication.

Remaining outcomes

None of the included trials assessed the effects of DAAs on ascites; variceal bleeding; hepato-renal syndrome; hepatic encephalopathy; liver transplantation; hepatocellular carcinoma; or histological improvement.

Our main results on DAAs on the market or under development are summarised in Summary of findings for the main comparison. Our main results on withdrawn DAAs are summarised in Summary of findings 2.

DISCUSSION

Summary of main results

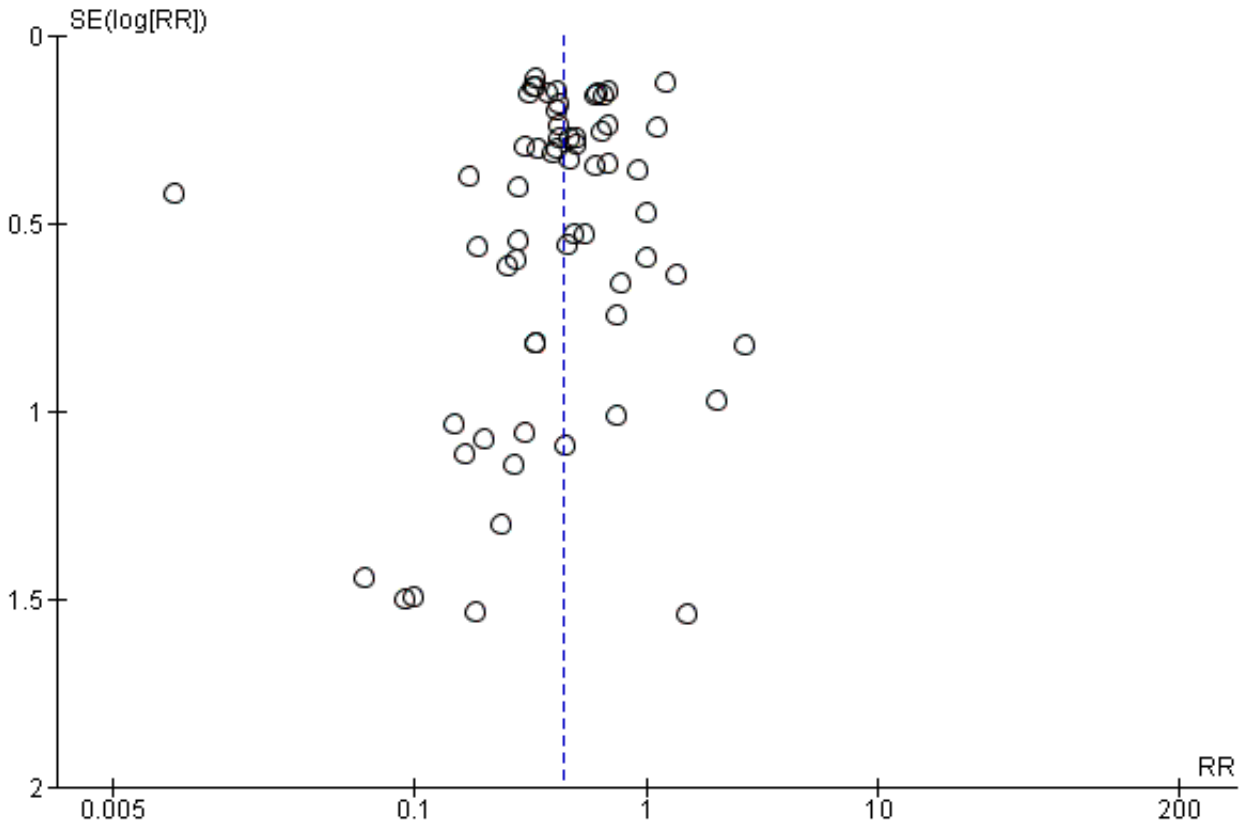
We included 138 trials randomising a total of 25,232 participants. All trials and outcome results were at high risk of bias and we assessed the evidence for all outcomes as very low or low quality. There were limited data on most of our clinical outcomes, that is, we could only identify clinical trial data on all-cause mortality and serious adverse events. Our primary results showed that when all DAAs on the market or under development were pooled in one analysis, DAAs did not seem to have any significant effects on the risk of serious adverse events. When meta-analysed separately, simeprevir was the only DAA showing evidence of a lower risk of a serious adverse event compared with placebo. However, Trial Sequential Analysis showed that there was not enough information to confirm or reject our anticipated intervention effect. The outcome result had high risk of bias, and when one trial with an extreme result was excluded from the analysis then the meta-analysis result showed no evidence of an effect. Withdrawn DAAs seemed to increase the risk of serious adverse events. There was not enough information to confirm or refute that DAAs have clinically relevant effects on other clinically relevant outcomes. Most of the included randomised clinical trials primarily focused on and assessed the effects of DAAs on sustained virological response. Our results confirm that DAAs seem to reduce the risk of no sustained virological response, but all the trial results were at high risk of bias. The clinical relevance of the results on sustained virological response has not been demonstrated from randomised evidence. Our main results are summarised in Summary of findings for the main comparison.

Overall completeness and applicability of evidence

We searched for published and unpublished trials irrespective of publication type, publication status, publication date, and language. We also searched bibliographies of both Cochrane and non-Cochrane reviews for any trials we missed.

The funnel plot for SVR shows possible asymmetry arising from data missing from the bottom right of the distribution (Figure 7). Although our analysis of SVR may be missing data from smaller trials (presumably showing smaller or no beneficial effects of DAAs) the impact of missing data on the results is negligible. The similar result obtained with a fixed-effect model (RR 0.42) does not indicate that small study effects exaggerate results of the primary analysis.

Figure 7. Funnel plot of comparison: 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), outcome: 3.1 Without sustained virological response.



Our primary analysis included all DAAs that are on the market or under development. We did not include withdrawn DAAs in the primary analysis because of the historical clinical relevance of assessing the effects of these DAAs. It might be that the different types of DAAs have different clinical effects, and we therefore also assessed each DAA separately. When analysing the effects of DAAs on risk of serious adverse events, tests for subgroup difference showed evidence of a difference, but when analysed separately, only simeprevir showed evidence of an effect. Nevertheless, the evidence of an effect depended on only one trial with an extreme

result and the meta-analysis result showed no evidence of a difference when this trial was excluded from the analysis. It might be that simeprevir has a beneficial effect on risk of serious adverse events but this effect needs to be shown in trials with low risk of bias in all domains. The remaining analyses showed that there was not enough information to confirm or refute that DAAs have beneficial or harmful effects on clinically relevant outcomes.

Our analyses showed that most DAAs seem to decrease the risk of no sustained virological response but, as mentioned, this result is based on trials at high risk of bias and the clinical relevance of results on this non-validated surrogate outcome is unknown.

Quality of the evidence

We have assessed the quality of the evidence for the results of three main outcomes (Summary of findings for the main comparison). The GRADE assessments showed that the quality if the evidence was very low for mortality (due to risk of bias and imprecision) and serious adverse events (due to risk of bias and indirectness). Trial Sequential Analysis of serious adverse events showed that the boundary for futility was crossed. Hence, there is firm evidence that DAAs versus control do not reduce the risk of serious adverse events by 20% or more (Figure 3). A post-hoc Trial Sequential Analysis showed that the acquired information was large enough to rule out that DAAs versus control reduce the risk of serious adverse events by 15% or more.

The quality of evidence for SVR was low due to risk of bias. We have reconsidered the issue of indirectness in relation to SVR and decided that indirectness is not applicable since we have not used it as a proxy for long-term cure in the review. Accordingly, there is a high risk that future trials may overturn the results of this present review. Reasons for the GRADE assessments are given in the footnotes of the Summary of findings for the main comparison. The boundary for benefit was crossed in the Trial Sequential Analysis of no sustained virological response showing that our analyses have sufficient sample size to indicate that DAAs reduce the risk of no sustained virological response.

Potential biases in the review process

Strengths

We included trials regardless of publication type, publication status, language, and choice of outcomes. We contacted all relevant trial authors if additional information was needed.

We used predefined up-to-date systematic review methodology and the methodology was not changed during the review process (Higgins 2011a; Jakobsen 2014a). We used Trial Sequential Analyses and adjusted our thresholds for significance to control the risks of random errors (Deeks 2011; Jakobsen 2014a), we thoroughly assessed the risks of bias of each trial to assess the risks of systematic errors ('bias') (Higgins 2011b; Jakobsen 2014a), and we used an eight-step procedure to assess if the thresholds for statistical and clinical significance were crossed (Jakobsen 2014a). This adds further robustness to our results and conclusions. We also tested the robustness of our results with sensitivity analyses (best-worst, worst-best, etc.) (Sterne 2011; Jakobsen 2014a).

We reported both aggregate as well as individual serious adverse events for all included trials reporting them. We also reported non-serious adverse events for all trials reporting them.

Limitations

Our systematic review has several limitations.

Our bias risk assessment showed that all trials were at high risk of bias. It is, therefore, highly probable that our review results are also biased, that is, that there is a great risk that our results overestimate benefit and underestimate harms (Jakobsen 2014a; Lundh 2012; Savović 2012a; Savović 2012b). This is the primary limitation of our review.

The Trial Sequential Analyses showed that, except for the primary analysis of the effects of DAAs on risk of serious adverse events, we did not have enough information to confirm or refute our anticipated clinical intervention effects. Not enough trials with a sufficient number of participants assessing clinically relevant outcomes have been conducted. It might be that limited statistical power has caused the multiple neutral meta-analysis results and that DAAs do have beneficial or harmful effects. Furthermore, we planned multiple secondary analyses and a large number of subgroup analyses, which lead to an increased risk of type I errors (Jakobsen 2014a). Hence, the risk of random type I errors is large in this review.

We included all types of DAAs (on the market or under development) in our primary analysis and the primary analysis of the results of the effects of DAAs on risk of serious adverse events showed that we had enough information to rule out a 20% relative risk reduction. It might be that different DAAs have different effects and that including certain DAAs in the analysis dilutes the beneficial or harmful effects of other DAAs. However, we found no signs of heterogeneity in our analyses, which indicates that all of the different DAAs seem to have no, or very limited, clinical effects on risk of serious adverse events. We chose primarily to focus on the overall pooled analysis of DAAs on the market or under development for two reasons: 1. a pooled analysis would have the largest statistical power as well as precision; and 2. it would be possible to compare the different DAAs in subgroup analysis if all types of DAA were included in this present review.

Our review is flawed by the lack of proper assessments of serious adverse events in observational studies and our lack of assessment of non-serious adverse events in randomised clinical trials as well as in observational studies. This gives our systematic review a significant tilt towards focusing on beneficial effects. We report the adverse events reported in the trials, but we decided post hoc to analyse the details on non-serious adverse events (due to their large number and prevalence) in a future publication focusing on this. For future systematic reviews, there is also a need to assess serious as well as non-serious adverse events reported in observational studies.

A potential limitation is the use of the composite outcome 'serious adverse events'. It is obvious that according to the definition of this outcome (see Primary outcomes) each component of this composite outcome will not necessarily have similar degrees of severity. This might bias the results of this outcome (Garattini 2016). For example, if certain more severe serious adverse events occur in one of the intervention groups and other less severe serious adverse events occur in the other intervention group, then there is a risk of overlooking actual severity differences between the compared groups when analysing this composite outcome (Garattini 2016). All-cause mortality would be the optimal patient-

relevant outcome with the fewest methodological limitations (Garattini 2016). However, due to limited information sizes it is rare that conclusions can be drawn assessing all-cause mortality and this is also the case in our present review. To obtain adequate statistical power it is often necessary to use composite outcomes; the potential limitations of using composite outcomes should always be considered when interpreting review results.

We chose pragmatically to only assess outcomes at one assessment time point, that is, the trial's result as provided at maximum follow-up. Most trials were only short-term results. Hence, our results can neither confirm nor reject that DAAs have clinical long-term effects, which is a further limitation of our present review results, especially because most of the harmful effects of hepatitis C take years to develop.

Agreements and disagreements with other studies or reviews

We have identified multiple reviews assessing the effects of different DAAs for chronic HCV. Tehey primarily focus on the effects of DAAs on sustained virological response showing, like we do, that DAAs increased sustained virological response. The previous reviews generally concluded that they were ‘safe’ (except for the withdrawn first-generation protease inhibitors). We summarise below the results of some of the identified reviews.

Lang 2013 meta-analysed the results of six randomised clinical trials involving a total of 2759 participants with chronic HCV genotype 1 infection. The results showed that the sustained virological response rate was significantly higher in the telaprevir-based regimens group (withdrawn DAA) than in the control group (OR 3.81; 95% CI 2.43 to 5.96). The results also showed that the relapse rate was significantly lower in the telaprevir-based regimens group than in the control group (RR 0.40; 95% CI 0.24 to 0.66). However, there was an increased risk of serious adverse events in the telaprevir-based regimens group (RR 1.45; 95% CI 1.12 to 1.87).

Basile 2014 meta-analysed the results of six trials involving 636 participants in the analyses. HCV genotype 1 participants had an overall 12-week sustained virological response of 66% (95% CI 57% to 73%) after 12 weeks of treatment. The outcome was significantly better for treatment-naive participants (70%) compared to treatment-experienced (10%). However, for HCV Genotype 2 and 3, there were similar 12-week sustained virological responses for both treatment-naive and treatment-experienced participants. The overall 12-week sustained virological response after 12 weeks of treatment was 75% (95% CI 71% to 78%).

Coco 2014 concludes that the first-generation protease inhibitors boceprevir (withdrawn DAA) and telaprevir (withdrawn DAA), administered with peg-IFN and RBV, significantly improved the sustained virological response both in treatment-naive and treatment-experienced participants with chronic genotype 1 hepatitis C. Nevertheless, their use was offset by the high incidence of adverse reactions.

Childs-Kean 2015 reviewed the effects of simeprevir and sofosbuvir. The review focused almost exclusively on results on sustained virological response. Simeprevir was studied with peg-IFN and RBV in seven published phase 3 trials, with overall efficacy rates of 59% to 100% (sustained virological response). Sofosbuvir was studied with RBV and with or without peg-IFN in six phase-3 trials with overall efficacy rates of 50% to 93% (sustained virological response). Rates of serious adverse events and early discontinuation were low in all phase-3 trials. The most common adverse events were fatigue, insomnia, diarrhoea, headache, and anaemia, and most were considered mild to moderate in severity. The authors concluded that sofosbuvir- and simeprevir-containing regimens were highly effective in obtaining sustained virological response and appeared safe for the treatment of chronic hepatitis C infection.

A narrative review presented an overview of the treatment of chronic HCV (Elbaz 2015). The authors concluded that an eradication of HCV seemed to be possible in the near future (Elbaz 2015).

Another narrative review concluded that DAAs were well-tolerated oral therapies with 'cure' rates of > 90% in most patient populations (Götte 2016). The authors focused on results on sustained virologic response and on the structural and mechanistic insights of DAAs (Götte 2016).

Conti 2016 have recently shown in an observational study that the occurrence of liver cancer is not reduced in people who obtained sustained virological response after treatment with DAAs. In addition, people previously treated for HCC still have a high risk of tumour recurrence in the short term, despite DAA treatment (Conti 2016).

Several studies have shown that achieving sustained virologic response in hepatitis C seems to be associated with improved clinical outcomes (Smith-Palmer 2015). However, as mentioned in Description of the condition the results of these observational studies should be interpreted with caution. Several of these non-randomised comparisons were between those who were treated and achieved a sustained virologic response and those who were treated but did not achieve a sustained virologic response; this study design has several major limitations with regard to making any inferences about causation. First of all, observational studies will always have confounding factors. Secondly, the two subgroups had different prognoses with regard to their baseline characteristics (since patients who develop sustained virologic response have characteristics that would predict that they are less likely to progress, such as limited fibrosis, lack of obesity, favourable IL B28 genotype, female sex, lack of HIV/alcohol, etc). Lastly, it is incorrect to attribute these different outcomes to treatment because all of the patients were treated. Comparison between those who achieved sustained virologic response and those never treated is confounded by the reason for the participants to have been, or not have been treated, and then further confounded by the problem with the differences in baseline characteristics

Our present review results confirm that DAAs seem to work on sustained virological response. Our present review results add to the previous findings that there are still limited data on the clinical effects of DAAs and that there seem to be no significant effects of DAAs on the risk of serious adverse events. We had too few data to assess the effects of DAAs on all-cause mortality. It must be noted that we, in this present review, have assessed the effects of DAAs on ‘serious adverse events’, and in our definition, adverse events are included in our analyses regardless of a possible causal link with the DAA. When an adverse event was ‘serious’ then we included it. Even though most of our results were short-term results, we were

not able to demonstrate the presence of major clinically beneficial or harmful effects of DAAs in people with chronic hepatitis C.

AUTHORS' CONCLUSIONS

Implications for practice

Most trials were designed to measure the short-term effect of direct-acting antiviral (DAA) treatment on virological response in adults with chronic hepatitis C, the majority of whom had not been treated previously. Rates of hepatitis C morbidity and mortality observed in the trials are low and we are uncertain as to how DAAs affect this outcome (very low quality evidence). Considered as one overall intervention, there is very low quality evidence that DAAs on the market or under development do not seem to influence the risk of serious adverse events. There is insufficient evidence to judge if DAAs have beneficial or harmful effects on other clinical outcomes for chronic HCV. DAAs may reduce the number of people with detectable virus in their blood, but we do not have sufficient evidence from randomised trials that enables us to understand how sustained virological response affects long-term clinical outcomes. We are unable to determine effects of long-term treatment from randomised evidence. All the trials and all of the outcome results were at high risk of bias, so there are risks that our results overestimate benefits and underestimate harms.

When analysed separately, simeprevir was the only DAA that showed evidence of an effect when assessing the risk of a serious adverse event, but this result was at high risk of bias and high risk of random errors. Withdrawn DAAs seemed to increase the risk of serious adverse events. Further evidence of long-term clinical benefit of DAAs on hepatitis C virus-related morbidity and mortality is needed to determine the efficacy of this treatment with greater certainty.

Implications for research

Randomised clinical trials assessing the clinical effects of DAAs are needed. Such trials should be conducted with low risk of bias, low risk of design errors, and low risk of random errors. Future trials ought to focus their assessments on patient-centred clinical outcomes.

Future randomised clinical trials ought to avoid the negative aspects we noted in the first 138 randomised clinical trials conducted on DAAs versus placebo or no intervention:

1. many of the trials employed skewed randomisation, so that more participants were randomised to DAA compared with placebo or no intervention. This reduces the power for the trials and makes it more difficult to assess rare outcomes such as clinical outcomes and serious adverse events;
2. most of the trials used as primary outcome a surrogate outcome, that is, sustained virological response. This outcome has not been subject to validation from randomised evidence;
3. most of the trials were at high risk of for-profit bias;
4. most of the trials were extremely short term, with trial intervention durations below 48 weeks and a follow-up period below 38 weeks;
5. too many of the trials had problems with randomisation and too short follow-up periods;
6. many of the trials used co-interventions that were not equally distributed among the participants in the experimental and control groups;
7. lack of trials assessing the effects of DAAs on quality of life;
8. many of the trials used multiple intervention arms making it hard or impossible to assess intervention effects properly; and
9. many of the trials reported adverse events in a way that it was hard or impossible to assess their severity.

Future trials ought to be designed according to the SPIRIT guidelines (Chan 2013) and reported according to the CONSORT guidelines (Schultz 2010). Threats to the validity of the evidence ought to be accounted for (Garattini 2016).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

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* Indicates the major publication for the study

ADVANCE 2011a1

Methods	Randomised phase III clinical trial
Participants	1088 participants **Countries:** Europe and USA **Inclusion criteria:** participants with HCV genotype 1 infection who had not received previous treatment 18-70 years of age and had HCV genotype 1 infection with evidence of chronic hepatitis, as confirmed by means of a liver biopsy within 1 year before screening for the study; people with compensated liver cirrhosis were eligible. **Exclusion criteria:** advanced liver disease, co-infection with HBV or HIV, HCC, other clinical relevant comorbidity. ALT> 5 x the ULN, total bilirubin > 2 mL/dL, albumin < 3.5 g/dL, international normalised ratio > 1.7, platelets < 90 x 10^9, haemoglobin < 12 g/dL (women) or < 13 g/dL (men).
Interventions	**Experimental group 1:** telaprevir (orally at a dose of 750 mg every 8 h) and peg-IFN α-2a (by subcutaneous injection at a dose of 180 µg per week) and RBV (orally at a dose of 1000 mg per day (in participants who weighed < 75 kg) or 1200 mg per day (in participants who weighed ≥ 75 kg)) for the entire 12 weeks followed by 4 weeks of placebo and peg-IFN–RBV (T12PR group). **Experimental group 2:** telaprevir (orally at a dose of 750 mg every 8 h) and peg-IFN α-2a (by subcutaneous injection at a dose of 180 µg per week) and RBV (orally at a dose of 1000 mg per day (in participants who weighed < 75 kg) or 1200 mg per day (in participants who weighed ≥ 75 kg) for 8 weeks and placebo with peg-IFN–RBV for 4 weeks (T8PR group). **Control group:** placebo with peg-IFN–RBV for 12 weeks, followed by 36 weeks of peg-IFN–RBV. Participants in the T12PR and T8PR groups who met the criteria for an extended RVR (defined as undetectable HCV RNA at weeks 4 and 12) received 12 additional weeks of treatment with peg-IFN–RBV alone, for a total treatment period of 24 weeks. Participants in the T12PR and T8PR groups who had detectable HCV RNA either at week 4 or at week 12 received 36 additional weeks of treatment with peg-IFN–RBV, for a total treatment period of 48 weeks. The group receiving peg-IFN α-2a and RBV alone (PR group) received placebo plus peg-IFN– RBV for 12 weeks, followed by peg-IFN–RBV alone for 36 additional weeks. **Co-intervention:** peg-IFN (subcutaneously at 180 µg/week) and RBV orally twice daily dosed according to body weight.
Outcomes	HCV RNA, safety assessment
Notes	We emailed Jacobson and colleagues on 21 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias)	Unclear risk	Described as being double-blinded but it was unclear how the blinding was performed

ADVANCE 2011a1 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

ADVANCE 2011a2

Methods	For characteristics see ADVANCE 2011a2	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb

ADVANCE 2011a2 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anderson 2014a1

Methods	Randomised clinical trial
Participants	74 participants were randomised **Sex:** 58 men, 16 women **Mean age:** 50.2 **Inclusion criteria:** treatment-naive adults 18-65 years of age with chronic HCV genotype 1 infection for > 6 months before study enrolment, with a BMI > 18 and < 35 kg/m^2. Chronic HCV infection was defined as 1 of the following: detectable HCV RNA or reactive HCV antibody > 6 months before enrolment; reactive antibody for HCV before screening and a liver biopsy > 6 months before enrolment demonstrating pathology consistent with HCV infection; and reactive HCV antibody or detectable HCV RNA before screening with an HCV risk factor (e.g. unsafe injection practices, blood transfusion before June 1992, receipt of clotting factor before 1987) that had emerged > 6 months before enrolment. In addition, participants had a liver biopsy result with histology consistent with HCV-induced liver damage and with no evidence of cirrhosis or liver pathology due to any cause other than chronic HCV within the 3-year period before study enrolment and participants had plasma HCV RNA level > 100.000 IU/mL at screening. **Exclusion criteria:** participants with METAVIR fibrosis score of 3 or 4 on liver biopsy, a positive test result for hepatitis B surface antigen or anti-HIV antibodies, a history of major depression within the 2 years before enrolment, or unresolved clinically significant diseases other than HCV were excluded from participation.
Interventions	**Experimental group:** 1. ABT-450/r 50/100 mg once a day + peg-IFN/RBV 2. ABT-450/r 100/100 mg once a day + peg-IFN/RBV 3. ABT-450/r 200/100 mg once a day + peg-IFN/RBV 4. ABT-072 100 mg once a day + peg-IFN/RBV 5. ABT-072 300 mg once a day + peg-IFN/RBV 6. ABT-072 600 mg once a day + peg-IFN/RBV 7. ABT-333 400 mg twice a day + peg-IFN/RBV 8. ABT-333 800 mg twice a day + peg-IFN/RBV **Control group:** placebo + peg-IFN/RBV **Co-intervention:** peg-IFN and RBV Participants were treated with ABT-450/r, ABT-333, or ABT-072 monotherapy for 3 days, followed by 81 days (12 weeks minus 3 days of monotherapy) of ABT-450/r, ABT-333, or ABT-072 combined with pegylated IFN/RBV (peg-IFN/RBV), followed by 36 weeks of peg-IFN/RBV alone.
Outcomes	**Primary outcomes:** maximal change from baseline in HCV RNA levels, maximum plasma concentration (Cmax) of ABT-450, time to maximum plasma concentration (Tmax) of ABT-450, area under the plasma concentration-time curve from 0-24 h (AUC24) post-dose of ABT-450, maximum plasma concentration (Cmax) of ritonavir, time to maximum plasma concentration (Tmax) of ritonavir, area under the plasma concentration-time curve from 0-24 h (AUC24) post-dose of ritonavir, maximum plasma concentration (Cmax) of ABT-072, time to maximum plasma concentration (Tmax) of ABT-072, area under the plasma concentration-time curve from 0-24 h (AUC24) post-dose of ABT-072, maximum plasma concentration (Cmax) of ABT-333, time to maximum plasma concentration (Tmax) of ABT-333, area under the plasma concentration-time curve from 0-12 h (AUC12) post-dose of abt-333.

Anderson 2014a1 *(Continued)*

	Secondary outcomes: percentage of participants with rapid virologic response (RVR) at week 4, percentage of participants with partial early virologic response (EVR) at week 12, Ppercentage of participants with complete early virologic response (cEVR) at week 12.
Notes	We emailed Anderson and colleagues on 20 April 2016 for unpublished data and additional information regarding allocation concealment, random sequence generation, and blinding of outcome but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators and participants were blinded to the study drug treatment regimen, but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants did not complete the study (19%), according to study protocol
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01074008)
Vested-interest bias	High risk	This study was funded by AbbVie
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anderson 2014a2

Methods	For characteristics see Anderson 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Anderson 2014a2 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators and participants were blinded to the study drug treatment regimen, but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants did not complete the study (19%), according to study protocol
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01074008)
Vested-interest bias	High risk	This study was funded by AbbVie
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anderson 2014a3

Methods	For characteristics see Anderson 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators and participants were blinded to the study drug treatment regimen, but it was not stated how the blinding was maintained.

Anderson 2014a3 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants did not complete the study (19%), according to study protocol
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01074008)
Vested-interest bias	High risk	This study was funded by AbbVie
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anderson 2014a4

Methods	For characteristics see Anderson 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators and participants were blinded to the study drug treatment regimen, but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants did not complete the study (19%), according to study protocol
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01074008)
Vested-interest bias	High risk	This study was funded by AbbVie

Anderson 2014a4 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anderson 2014a5

Methods	For characteristics see Anderson 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators and participants were blinded to the study drug treatment regimen, but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants did not complete the study (19%), according to study protocol
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01074008)
Vested-interest bias	High risk	This study was funded by AbbVie
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anderson 2014a6

Methods	For characteristics see Anderson 2014a1
Participants	

Anderson 2014a6 *(Continued)*

Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators and participants were blinded to the study drug treatment regimen, but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants did not complete the study (19%), according to study protocol
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01074008)
Vested-interest bias	High risk	This study was funded by AbbVie
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anderson 2014a7

Methods	For characteristics see Anderson 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Anderson 2014a7 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators and participants were blinded to the study drug treatment regimen, but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants did not complete the study (19%), according to study protocol
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01074008)
Vested-interest bias	High risk	This study was funded by AbbVie
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anderson 2014a8

Methods	For characteristics see Anderson 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators and participants were blinded to the study drug treatment regimen, but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Anderson 2014a8 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants did not complete the study (19%), according to study protocol
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01074008)
Vested-interest bias	High risk	This study was funded by AbbVie
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anonymous (PPI-461) 2011a1

Methods	Randomised clinical trial
Participants	24 treatment-naive participants were randomised **Inclusion criteria:** 18-65 years male and female, genotype 1, treatment-naive. Female participants must be surgically sterile or 2 years post-menopausal and are required to take a pregnancy test. BMI 18-32 kg/m2, chronically infected with HCV genotype 1. Serum HCV RNA > 5 log 10 IU/mL. No previous treatment with IFNIFN, peg-IFN, RBV or any investigational HCV antiviral agents. No history or signs of decompensated liver disease. No known history of cirrhosis, no co-infection with HBV or HIV. No history of any medical condition that may interfere with absorption, distribution or elimination of study drug or with the clinical and laboratory assessments in this study. No history of alcohol abuse, or illicit drug use within 2 years prior to screen or enrolment in a methadone maintenance programme (unless he/she has been enrolled in the programme for at least 3 months with good compliance, stable psychosocial circumstances and no known current risks for recidivism).
Interventions	**Experimental group:** 50 mg PPI-461 once a day, 100 mg PPI-461 once a day, 200 mg PPI-461 once a day for 3 days **Control group:** placebo 2 weeks' follow-up **Co-intervention:** none
Outcomes	**Primary outcomes:** safety and tolerability as measured by clinical AE and laboratory assessments (time frame: up to study day 16, 14 days after the last dose of PPI-461). Antiviral effects of PPI-461 measured by HCV RNA levels and pharmacokinetics measured by plasma concentrations of PPI-461 concentrations.
Notes	This is an unpublished study, only results from 2 abstracts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Anonymous (PPI-461) 2011a1 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial is described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No main publication, no drop-outs
Selective reporting (reporting bias)	Unclear risk	Outcomes are only published in the protocol
Vested-interest bias	High risk	Lead sponsor is Presidio Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anonymous (PPI-461) 2011a2

Methods	For characteristics see Anonymous (PPI-461) 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial is described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No main publication, no drop-outs

Anonymous (PPI-461) 2011a2 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Outcomes are only published in the protocol
Vested-interest bias	High risk	Lead sponsor is Presidio Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Anonymous (PPI-461) 2011a3

Methods	For characteristics see Anonymous (PPI-461) 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial is described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No main publication, no drop-outs
Selective reporting (reporting bias)	Unclear risk	Outcomes are only published in the protocol
Vested-interest bias	High risk	Lead sponsor is Presidio Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

ASPIRE 2014

Methods	Randomised phase IIb clinical trial
Participants	462 participants Location**:** Europe and USA **Inclusion criteria:** participants infected with HCV genotype 1 who had failed to respond to previous peg-IFN/RBV treatment, adult participants, aged 18-70 years, chronically infected with HCV genotype 1 and with plasma HCV RNA > 10,000 IU/mL at screening. All participants had to have received at least 1 prior course of peg-IFN/RBV for 12 consecutive weeks and not discontinued therapy due to tolerability. **Exclusion criteria:** decompensated liver disease, any other liver disease of non-HCV aetiology, and infection/co-infection with nongenotype 1 HCV.
Interventions	**Experimental group:** 1. simeprevir 100 mg plus peg-IFN/RBV 12 weeks followed by 36 weeks of peg-IFN/RBV 2. simeprevir 150 mg plus peg-IFN/RBV 12 weeks followed by 36 weeks of peg-IFN/RBV 3. simeprevir 100 mg plus peg-IFN/RBV 24 weeks followed by 24 weeks of peg-IFN/RBV 4. simeprevir 150 mg plus peg-IFN/RBV 24 weeks followed by 24 weeks of peg-IFN/RBV 5. simeprevir 100 mg plus peg-IFN/RBV 48 weeks 6. simeprevir 150 mg plus peg-IFN/RBV 48 weeks **Control group:** 48 weeks of simeprevir-matched placebo plus peg-IFN/RBV **Co-intervention:** peg-IFN (subcutaneously at 180 µg/week) and RBV orally (1000 mg or 1200 mg/day, depending on body weight). For all participants, the 48-week treatment period was followed by post-treatment follow-up for up to 72 weeks after treatment initiation.
Outcomes	HCV RNA, safety assessment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used a computer random-generation code
Allocation concealment (selection bias)	Low risk	The trial used a interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated on ClinicalTrials.gov were reported (NCT00980330)

ASPIRE 2014 *(Continued)*

Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

ATLAS 2013

Methods	Randomised phase II clinical trial
Participants	225 participants **Inclusion criteria:** HCV treatment-naïve adults aged 18 years or older with serologic evidence of chronic HCV genotype 1 infection, a serum HCV RNA level 50,000 IU/mL, and an absence of advanced fibrosis or cirrhosis (METAVIR score of F3-4). **Exclusion criteria:** participants infected with HCV non-1 genotypes or co-infected with HBV or with HIV were excluded, as were participants with liver disease attributable to a cause other than HCV infection, cardiac or renal disease, severe psychiatric disease, uncontrolled seizures, severe retinopathy, immunologically-mediated disease, poorly controlled diabetes, or who were pregnant or breastfeeding. Participants were also excluded if they had a haemoglobin concentration < 11 g/dL (women), or < 12 g/dL (men); neutrophil count < 1.5 x 109 cells/L; platelet count < 90 x 109 cells/L; serum creatinine concentration > 1.5 times the ULN); or BMI (calculated as kg/m2) < 18 or > 36. The use of agents that could interfere with the metabolism of danoprevir was prohibited.
Interventions	**Experimental group:** 1. dareprevir (orally at a dose of 300 mg every 8 h) and peg-IFN α-2a (by subcutaneous injection at a dose of 180 µg per week) and RBV (orally at a dose of 1000 mg per day (in participants who weighed < 75 kg) or 1200 mg per day (in participants who weighed ≥ 75 kg)) for the entire 12 weeks 2. dareprevir (orally at a dose of 600 mg every 12 hours) and peg-IFN α-2a (by subcutaneous injection at a dose of 180 µg per week) and RBV (orally at a dose of 1000 mg per day (in participants who weighed < 75 kg) or 1200 mg per day (in participants who weighed ≥ 75 kg)) for the entire 12 weeks 3. dareprevir (orally at a dose of 900 mg every 12 h) and peg-IFN α-2a (by subcutaneous injection at a dose of 180 µg per week) and RBV (orally at a dose of 1000 mg per day (in participants who weighed < 75 kg) or 1200 mg per day (in participants who weighed ≥ 75 kg or more)) for the entire 12 weeks **Control group:** placebo with peg-IFN–RBV for 24 or 48 weeks **Co-intervention:** peg-IFN (subcutaneously at 180 µg/week) and RBV orally twice daily dosed according to body weight
Outcomes	HCV RNA (SVR), safety assessment
Notes	we emailed Marcellin and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial used a computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Interactive voice/web response system

ATLAS 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as "partial-blind labeling"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed (NCT00963885)
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Bacon 2011a1

Methods	Parallel-group, randomised, placebo-controlled, double-blind study (RESPOND-2)(NCT00708500)
Participants	403 participants **Inclusion criteria:** chronic hepatitis C infection genotype 1 HCV RNA ≥ 10,000 IU/mL, demonstrated responsiveness to IFN (minimum duration of therapy 12 weeks); non-response defined as a decrease in HCV RNA of at least 2 $\log_{10}$ IU/mL by week 12, but with detectable HCV RNA during the therapy period; relapse defined as an undetectable HCV RNA at end of treatment, but without subsequent attainment of SVR. A liver biopsy with histology consistent with chronic hepatitis C, age ≥ 18 years, weight between 40-125 kg, signed informed consent, acceptable method of contraception for the participant and participant's partner(s) for at least 2 weeks before day 1 and continue until at least 6 months after treatment termination. **Exclusion criteria:** Hepatitis B infection, HIV infection, other causes of liver disease, decompensated liver disease, uncontrolled diabetes mellitus, a severe psychiatric disorder, active substance abuse, active or suspected malignancy, or a history of malignancy within last 5 years, pregnant or nursing women, severe AE during prior treatment, seizure disorder, cerebrovascular diseases, cardiovascular disease, autoimmune diseases, prior organ transplantation, haemoglobinopathies, coagulopathies, abnormal levels of serum bilirubin, albumin, and creatinine, haemoglobin < 120 g/L (women) and < 130 g/L (men), neutrophil count < 1500/mm^3, platelet count < 100,000/mm^3. **Group 1:** 80 participants Age, mean (years): 52.9 Sex: 58 men (72%), 22 women (28%) Race, n(%): white: 62(84), black: 12(15), other: 1(1) Region, n(%): North America: 51(64), European Union: 29(36). Latin America: 0. BMI, mean ± SD (kg/m^2): 28.2 ± 4.3 HCV subtype, n(%): 1a: 46(58), 1b: 34(42), missing data: 0 HCV RNA > 800,000 IU/mL, n(%): 65(81)

Bacon 2011a1 *(Continued)*

	METAVIR fibrosis score, n(%): 0, 1, or 2: 61(76), 3 or 4: 15(19) Cirrhosis, n(%): 10(12) Previous therapy, n(%): peg-IFN alpha-2a: 42(53), peg-IFN alpha-2b: 38(48) Prior non-response, n(%): 29(36) Prior relapse, n(%): 51(64) **Group 2:** 162 participants Age, mean (years): 52.9 Sex: 98 men (60%), 64 women (40%) Race, n(%): white: 142(88), black: 18(11), other: 2(1). Region, n(%): North America: 115(71), European Union: 46(28), Latin America: 1(1). BMI, mean ± SD (kg/m^2): 28.8 ± 4.6 HCV subtype, n(%): 1a: 94(58), 1b: 66(41), missing data: 2(1) HCV RNA > 800,000 IU/mL, n(%): 147(91) METAVIR fibrosis score, n(%): 0, 1, or 2: 117(72), 3 or 4: 32(20) Cirrhosis, n(%): 17(10) Previous therapy, n(%): peg-IFN alpha-2a: 79(49), peg-IFN alpha-2b: 83(51) Prior non-response, n(%): 57(35) Prior relapse, n(%): 105(65) **Group 3:** 161 participants Age, mean (yr.): 52.3 Sex: 112 men (70%), 49 women (30%) Race, n(%): white: 135(84), black: 19(12), other: 7(4) Region, n(%): North America: 119(74), European Union: 42(26), Latin America: 0. BMI, mean ± SD (kg/m^2): 28.2 ± 4.6 HCV subtype, n(%): 1a: 96(60), 1b: 61(38), missing data, 4(2) HCV RNA > 800,000 IU/mL, n(%): 141(88) METAVIR fibrosis score, n(%): 0, 1, or 2: 119(74), 3 or 4: 31(20) Cirrhosis, n(%): 17(10) Previous therapy, n(%): pegIFN alpha-2a: 79(49), peg-IFN alpha-2b: 83(51) Prior non-response, n(%): 57(35) Prior relapse, n(%): 105(65)
Interventions	**Experimental group:** Group 2: oral boceprevir 800 mg thrice-daily to be taken in with food and with an interval of 7-9 h, in 4 capsules of 200 mg each, beginning at week 5 for a total of 32 weeks (if HCV RNA undetectable at week

Bacon 2011a1 *(Continued)*

	8 and 12, treatment was terminated at week 36; if HCV RNA detectable at week 8 participants received placebo + peg-IFN + RBV for an additional 12 weeks). Group 3: oral boceprevir 800 mg thrice-daily to be taken in with food and with an interval of 7-9 h, in 4 capsules of 200 mg each, beginning at week 5 for a total of 44 weeks **Control group:** Group 1: boceprevir-matched placebo beginning at week 5 for a total of 44 weeks. **Co-interventions:** Group 1 and 3: peg-IFN alpha-2b 1.5 µg/kg body weight subcutaneously once weekly and weight-based oral RBV at a divided daily dose of 600 to 1400 mg for a total of 48 weeks Group 2: peg-IFN alpha-2b 1.5 µg/kg body weight subcutaneously once weekly and weight-based oral RBV at a divided daily dose of 600 to 1400 mg for 36 weeks (if HCV RNA undetectable at week 8 and 12), and for 48 weeks if (HCV RNA detectable at week 8, but undetectable at week 12).
Outcomes	**Primary outcome:** achievement of SVR (undetectable HCV RNA at week 24). **Secondary outcome:** achievement of SVR in randomised participants who received at least 1 dose of experimental study drug or placebo. Proportion of participants with EVR (undetectable HCV RNA at week 2, 4, 8, or 12) who achieved SVR. Proportion of participants with undetectable HCV RNA at week 12. Proportion of participants with undetectable HCV RNA at 72 weeks after randomisation.
Notes	Group 2 received a similar, but not equal co-intervention as Groups 1 and 3.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Allocation of participants through interactive voice-response system in a 1:2:2 ratio
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A boceprevir-matched placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not mentioned if the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Treatment discontinuation due to AE was 2% to 12%. Seems no other drop-outs occurred.
Selective reporting (reporting bias)	Low risk	A study protocol was published prior to randomisation (NCT00708500). All pre-specified outcomes were reported on.
Vested-interest bias	High risk	Trial was sponsored by a pharmaceutical company (Schering-Plough/Merck). The company was directly involved in trial design and managing, data analysis, and writing of article.
Other bias	Low risk	Seems there were no other potential sources of bias.

Bacon 2011a2

Methods	For characteristics see Bacon 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Allocation of participants through interactive voice-response system in a 1:2:2 ratio
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A boceprevir-matched placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not mentioned if the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Treatment discontinuation due to AE was 2% to 12%. Seems no other drop-outs occurred.
Selective reporting (reporting bias)	Low risk	A study protocol was published prior to randomisation (NCT00708500). All pre-specified outcomes were reported on.
Vested-interest bias	High risk	Trial was sponsored by a pharmaceutical company (Schering-Plough/Merck). The company was directly involved in trial design and managing, data analysis, and writing of article.
Other bias	Low risk	Seems there were no other potential sources of bias.

Basu 2014a

Methods	Randomised clinical trial
Participants	60 adult participants **Sex:** not described **Mean age:** not described

Basu 2014a *(Continued)*

	Inclusion criteria: chronic hepatitis C and with a psychiatric disorder (n = 60, schizophrenia 20/60 (33.3%)), major depression 15/60 (25%), bipolar disorder 20/60 (33.3%), and prior suicidal attempts with depression 5/60 (8.3%). **Exclusion criteria:** Renal failure with CrCl < 30, sickle cell, thalassaemic syndromes, haemolytic syndrome, co-infections (HBV, HIV), or CHF NYHA Stage IV.
Interventions	**Experimental group:** Group 1: simeprevir 150 mg and RBV 1000 mg daily Group 3: simeprevir 150 mg and vitamin D 5000 mg daily. **Control group:** placebo and RBV 1000 mg daily **Co-intervention:** Sofosbuvir 400 mg
Outcomes	Antiviral effect
Notes	Email was sent to Basu and colleagues on 06 June 2016 for additional information on allocation sequence generation and concealment, blinding, incomplete outcome data, protocol, full publication, study sponsor, death, SAE, SVR but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial is described as open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial is described as open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how many participants dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol could be found
Vested-interest bias	Unclear risk	It was unclear how the trial was funded
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Bavisotto 2007

Methods	Randomised clinical trial

Bavisotto 2007 *(Continued)*

Participants	68 participants **Sex:** 20 men, 11 women (only reported in Bavisotto trial) **Mean age:** 43.6 years **Country:** USA **Inclusion criteria:** Chronically infected with HCV genotype 1 (genotype-1) without cirrhosis. 18-60 years of age and HCV treatment-naive.
Interventions	**Experimental group:** ascending doses of GS-9190 (40, 120, 240, 240-with food, or 480 mg) orally for 8 days. **Control group:** placebo orally for 8 days.
Outcomes	Adverse events, GS-9190 concentration, HCV RNA
Notes	No data could be used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be found
Vested-interest bias	High risk	Sponsored by Gilead
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Benhamou 2013a1

Methods	Randomised clinical trial
Participants	24 participants

Benhamou 2013a1 *(Continued)*

	Sex: 15 men, 9 women **Median age:** 45.5 years **Country:** France **Inclusion criteria:** chronic G4 HCV infection. HCV-infected treatment-naive participants aged 18–65 years and in good health (except for chronic G4 HCV infection) were eligible if they had a plasma HCV RNA load of > 10,000 IU/mL, an absolute neutrophil count of ≥ 1500 neutrophils/mm3, and a platelet count of ≥ 100,000 platelets/mm3. **Exclusion criteria:** contraindications to IFN (peg-IFN in particular) or RBV treatment; history or evidence of cirrhosis, end-stage liver disease, or decompensated liver disease (as shown by screening laboratory results); HIV or HBV co-infection; history of alcohol or illicit drug use; and pregnancy/current breast-feeding
Interventions	**Experimental group 1:** oral 750 mg of telaprevir 3 times daily for 2 weeks **Experimental group 2:** oral 750 mg of telaprevir 3 times daily for 2 weeks + peg-IFN α-2a 180 µg once weekly, and RBV 1000–1200 mg/day (weight-based) **Control group:** placebo + peg-IFN α-2a 180 µg once weekly, and RBV 1000–1200 mg/day (weight-based) for 2 weeks **Co-intervention:** after the 2 weeks of treatment, all participants received peg-IFN α-2a 180 µg once weekly, and RBV 1000–1200 mg/day (weight based) (48 weeks for experimental group 1, and 46 weeks for experimental group 2 and control group)
Outcomes	Efficacy assessment, virology assessment, safety and pharmacokinetic assessment
Notes	NCT00580801

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described adequately (computer-based)
Allocation concealment (selection bias)	Unclear risk	Not described adequately (computer-based)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was only partially blinded. The participants in the telaprevir group without peg-IFN and RBV were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was only partially blinded. The participants in the telaprevir group without peg-IFN and RBV were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	< 5% dropped out (1 person)
Selective reporting (reporting bias)	Unclear risk	No predefined outcomes were stated in the protocol (NCT00580801)
Vested-interest bias	High risk	The trial was funded by Janssen Pharmaceuticals and Vertex Pharmaceuticals

Benhamou 2013a1 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Benhamou 2013a2

Methods	For characteristics see Benhamou 2013a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described adequately (computer-based)
Allocation concealment (selection bias)	Unclear risk	Not described adequately (computer-based)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was only partially blinded. The participants in the telaprevir group without peg-IFN and RBV were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was only partially blinded. The participants in the telaprevir group without peg-IFN and RBV were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	< 5% dropped out (1 person)
Selective reporting (reporting bias)	Unclear risk	No predefined outcomes were stated in the protocol (NCT00580801)
Vested-interest bias	High risk	The trial was funded by Janssen Pharmaceuticals and Vertex Pharmaceuticals.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Boehringer Ingelheim 2010a

Methods	Randomised clinical trial
Participants	34 adult participants

Boehringer Ingelheim 2010a *(Continued)*

	Inclusion criteria: chronic HCV infection with genotype 1 (1a, 1b or mixed 1a/1b), with an HCV VL ≥ 100,000 IU/ml at screening. For treatment-naive participants, no prior therapy with IFN, peg-IFN, or RBV was allowed. For treatment-experienced participants, virological failure with peg-IFN/RBV treatment was to be confirmed. treatment-experienced participants without cirrhosis required histological evidence within 24 months prior to trial enrolment of chronic necroinflammatory activity or the presence of fibrosis; treatment-experienced participants with compensated cirrhosis required histological evidence of cirrhosis due to HCV infection, without evidence of decompensation. **Exclusion criteria:** HCV infection of mixed genotype or had been treated previously with at least one dose of any protease.
Interventions	**Experimental group:** oral BI 201335 NA, 20 mg, 48 mg, 120 mg, or 240 mg once daily. **Control group:** placebo. **Co-intervention:** peg-IFN/RBV.
Outcomes	Virological response, pharmacokinetics, safety
Notes	Unpublished data only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being blinded, but it was unclear how this was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being blinded, but it was unclear how this was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 5% dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Boehringer Ingelheim 2010b

Methods	Randomised clinical trial
Participants	10 adult participants

Boehringer Ingelheim 2010b *(Continued)*

	Inclusion criteria: with diagnosis of cirrhosis and chronic HCV (genotype 1) infection with a VL greater than 50,000 copies mRNA/ml serum. **Country:** Germany
Interventions	**Experimental group:** oral 200 mg twice daily for 2 days. **Control group:** placebo.
Outcomes	Efficacy assessment, safety assessment
Notes	Unpublished data only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Bronowicki 2013a1

Methods	Randomised clinical trial
Participants	48 adult participants **Sex:** 35 men, 12 women **Mean age:** 48.5 years **Inclusion criteria:** 18-70 years old with Chronic HCV genotype 1 infection and HCV RNA above 100,000 IU/mL. Participants had no prior treatment or < 4 weeks of total exposure to RBV or peg-IFN-based ther-

Bronowicki 2013a1 *(Continued)*

	apy. Participants had to be non-cirrhotic, documented by liver biopsy obtained within 24 months before randomisation. **Exclusion criteria:** advanced liver disease, co-infection with HBC or HIV, hepatocellular carcinoma, other clinical relevant comorbidity. ALT > 5 x the ULN, total bilirubin > 2 mL/dL, albumin < 3.5 g/dL, international normalised ratio > 1.7, platelets < 90x10^9, haemoglobin < 12 g/dL (women) or < 13 g/dL (men).
Interventions	**Experimental group 1:** oral asunaprevir (200 mg) twice daily for 48 weeks. **Experimental group 2:** oral asunaprevir (600 mg) twice daily for 48 weeks. **Experimental group 3:** oral asunaprevir (600 mg) once daily for 48 weeks. **Control group:** placebo 48 weeks. **Co-intervention:** peg-IFN (subcutaneously at 180 µg/week) and RBV orally twice daily dosed according to body weight.
Outcomes	Proportion of participants with undetectable HCV RNA at week 4 and 12, SAE, AE, mortality, sustained virological response.
Notes	Experimental group 1 vs control. We contacted trial authors on 20 April 2016 for additional information on allocation concealment, specifics of the blinding, what SAE were experienced, and how they dealt with missing data, reached required sample size but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was stated that investigators and participants were blinded to treatment assignment throughout the study but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The sponsor was blinded to treatment assignment until the primary end point analysis which was at 12 weeks and we used data at week 24.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants had missing data and how the trial handled participants with missing data
Selective reporting (reporting bias)	Low risk	All outcomes stated in the pre published protocol (NCT01030432) were reported
Vested-interest bias	High risk	The study was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Bronowicki 2013a2

Methods	For characteristics see Bronowicki 2013a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was stated that "Investigators and participants were blinded to treatment assignment throughout the study" but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The sponsor was blinded to treatment assignment until the primary end point analysis which was at 12 weeks and we used data at week 24.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants had missing data and how the trial handled participants with missing data
Selective reporting (reporting bias)	Low risk	All outcomes stated in the pre published protocol (NCT01030432) were reported
Vested-interest bias	High risk	The study was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Bronowicki 2013a3

Methods	For characteristics see Bronowicki 2013a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bronowicki 2013a3 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was stated that investigators and participants were blinded to treatment assignment throughout the study but it was not stated how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The sponsor was blinded to treatment assignment until the primary end point analysis which was at 12 weeks and we used data at week 24.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants had missing data and how the trial handled participants with missing data
Selective reporting (reporting bias)	Low risk	All outcomes stated in the pre published protocol (NCT01030432) were reported
Vested-interest bias	High risk	The study was funded by Bristol Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Bronowicki 2014

Methods	Randomised clinical trial
Participants	238 adult participants **Sex:** 153 men, 85 women **Mean age:** 47.7 years **Inclusion criteria:** 18–70 years, with chronic HCV genotype 1 or 4 infection and HCV RNA P100,000 IU/mL. Participants had to have ALT < 5 ULN and no history or evidence of hepatic decompensation. Compensated cirrhotic participants (genotype 1 only) were eligible with a liver biopsy documenting cirrhosis from any period prior to randomisation. For non-cirrhotic participants, absence of cirrhosis had to be documented by a liver biopsy obtained within 24 months pre-randomisation. **Exclusion criteria:** prior exposure to anti-HCV agents, co-infection with HBV or HIV, and chronic liver disease other than HCV.
Interventions	**Experimental group:** 200 mg asunaprevir twice a day for 12 or 24 weeks. **Control intervention:** placebo twice a day for 12 weeks. **Co-intervention:** peg-IFNa-2a administered subcutaneously at 180 lg per week, and oral RBV twice a day dosed by body weight (< 75 kg, 1000 mg daily; P75 kg, 1200 mg daily).
Outcomes	SAE, AEs, discontinuations due to AEs, eRVR at week 4 and 12, SVR24, RVR at week 4, complete eRVR, SVR 12, resistant variants associated with virologic failure.

Bronowicki 2014 *(Continued)*

Notes	At week 12, asunaprevir-treated participants who achieved a protocol-defined response (HCV RNA < LLOQ at week 4 and undetectable at week 10 were re-randomised (1:1) to continue triple therapy with asunaprevir plus peg-IFNα/RBV for a total of 24 weeks (24-Triple) or to receive placebo plus peg-IFNα/RBV for an additional 12 weeks (12-Triple + 12; Fig. 1). Asunaprevir-treated participants without PDR and those initially assigned to placebo received placebo plus peg-IFNα/RBV from week 13 to 24. At week 24, PDR-positive participants who received 24-Triple or 12-Triple + 12 stopped treatment and were followed through week 48. PDR-negative participants and those initially assigned to placebo were switched to open-label peg-IFNα/RBV through week 48 and followed through week 72. We report re-randomisation in Bronowicki 2014a. We contacted the trial authors on 25 February 2016 by email jp.bronowicki@chu-nancy.fr about allocation concealment, SAE at maximum follow-up, specific SAE at maximum follow-up, how the authors accounted for data of missing participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators and participants were blinded to treatment assignment through week 24; the sponsor was blinded through week 12. It was unknown how the blinding was maintained. Additionally, some of the participants had open-label peg-IFNα/RBV
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators and participants were blinded to treatment assignment through week 24; the sponsor was blinded through week 12. It was unknown how the blinding was maintained. Additionally, some of the participants had open-label peg-IFNα/RBV
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were under 5% dropouts
Selective reporting (reporting bias)	Low risk	The outcomes stated in the pre published protocol (ClinicalTrials.gov:NCT01030432) were reported on
Vested-interest bias	High risk	Funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

C-EDGE CO STAR 2015

Methods	Randomised clinical trial
Participants	301 participants **Sex:** 228 men and 73 women **Mean age:** 47 years

C-EDGE CO STAR 2015 *(Continued)*

	Inclusion criteria: documented chronic HCV genotype 1 (genotype1), genotype4, or genotype6 infection with no evidence of genotype2 or genotype3 or non-typeable genotypes and HCV RNA confirmed by screening lab results prior to randomisation on opiate substitution therapy (methadone, levamethadone, buprenorphine, naloxone, naltrexone) for at least 3 months prior to screening, treatment-naive to all HCV therapies. HIV-infected participants enrolled in this study had to meet following criteria: Documented HIV infection, naive to treatment with any antiretroviral therapy or on HIV antiretroviral therapy for at least 8 weeks prior to study entry using a dual nucleoside reverse transcriptase inhibitor backbone of tenofovir or abacavir and either emtricitabine or lamivudine plus raltegravir (or dolutegravir or rilpivirine). Dose modifications or changes in antiretroviral therapy during the 4 weeks prior to study entry (Day 1) were not permitted. Cluster of differentiation 4 (CD4+) T-cell count > 200 cells/mm^3 if on antiretroviral therapy or > 500 cell/mm^3 if antiretroviral therapy treatment-naive undetectable plasma HIV-1 RNA at least 8 weeks prior to screening if on antiretroviral therapy or < 50,000 copies/mL if antiretroviral therapy treatment-naive. Participants with HIV-1 infection and on antiretroviral therapy must have at least 1 viable antiretroviral regimen alternative beyond their current regimen in the event of HIV virologic failure or the development of anti-retroviral drug resistance Women who are of reproductive potential had to agree to avoid becoming pregnant while receiving study drug and for 14 days after the last dose of study drug by complying with 1 of the following: (1) practice abstinence from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. **Exclusion criteria:** evidence of decompensated liver disease. For participants with cirrhosis, participants who are Child-Pugh Class B or C or who have a Pugh-Turcotte score > 6 Is co-infected with HBV. Has cirrhosis and liver imaging within 6 months of Day 1 showing evidence of HCC or is under evaluation for HCC. Currently using or intends to use barbiturates during the treatment period of this study. Is a female and is pregnant or breast-feeding, or expecting to conceive or donate eggs from Day 1 or anytime during treatment, and 14 days after the last dose of study medication, or longer if dictated by local regulations. Any medical condition requiring or likely to require chronic systemic administration of corticosteroids, Tumor Necrosis Factor-antagonists, or other immunosuppressant drugs during the course of the trial. Evidence or history of chronic hepatitis not caused by HCV.
Interventions	**Experimental group:** oral 100 mg of grazoprevir and 50 mg of elbasvir for 12 weeks. **Control group:** placebo.
Outcomes	Safety assessment, HCV RNA (virological failure).
Notes	Abstract only (still ongoing). Only data for the first 12 weeks could be used, since the control group received the same DAA in the following 12 weeks. (NCT02105688).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias)	Unclear risk	No description of dropouts after 12 weeks for the control group.

C-EDGE CO STAR 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Only an abstract could be found, and no data on SVR12 and SVR24 were presented. However the trial was still stated as ongoing. (NCT02105688)
Vested-interest bias	High risk	The trial was funded by Merck
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

C-EDGE TN 2015

Methods	Randomised clinical trial
Participants	421 participants **Sex:** 227 men, 194 women **Mean age:** 52.6 years **Countries:** Australia, Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Sweden, Taiwan, and USA **Inclusion criteria:** treatment-naive cirrhotic and non-cirrhotic adults (aged > 18 years) with HCV RNA levels > 104 IU/mL were eligible. Hepatic fibrosis was staged by biopsy or noninvasive assessment. **Exclusion criteria:** decompensated liver disease, HCC, HIV or HBV co-infection, uncontrolled diabetes mellitus (haemoglobin A1c level > 10%), elevated prothrombin time unrelated to anticoagulation, creatinine clearance < 50 mL/min, haemoglobin level < 95 g/L, thrombocytopenia (platelet count < 50 × 109 cells/L), aminotransferase levels more than 10 times the ULN, or hypoalbuminaemia (albumin level < 30 g/L).
Interventions	**Experimental group:** oral 100 mg of grazoprevir and 50 mg of elbasvir for 12 weeks. **Control group:** placebo.
Outcomes	HCV RNA, safety assessment.
Notes	Only data for the first 12 weeks could be used, since the control group received the same DAA in the following 12 weeks. We emailed Zeuzem and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial used a "computer-generated random allocation schedule"
Allocation concealment (selection bias)	Low risk	The trial used a "central interactive voice-response system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and personnel were blinded to treatment assignment for the first 12 weeks (and we used the data from this time point)

C-EDGE TN 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The sponsors performing the analyses were blinded to treatment assignment for the first 12 weeks (and we used the data from this time point)
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 5% dropped out after 12 weeks
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed (NC02105467)
Vested-interest bias	High risk	The trial was funded by Merck-Sharp which performed the analyses
Other bias	Low risk	Trial seems to be free of other potential sources of bias

Chandra 2006a

Methods	Randomised clinical trial
Participants	An unknown amount of participants **Sex:** unknown **Mean age:** unknown **Inclusion criteria:** chronic HCV infection (> 6 months) and were treatment-naive. Participants aged 18-64 years with ≥ 104 IU/mL HCV RNA levels were enrolled in sequential, ascending dose cohorts of up to 16 participants (12 active, 4 placebo) per cohort.
Interventions	**Experimental group:** participants received 50, 100, 250, 500, 1000, or 1500 mg oral doses of HCV-796 or placebo given as monotherapy twice daily. **Control group:** placebo twice a day. **Co-intervention:** none.
Outcomes	Most frequent AE, dose-limiting toxicities or serious treatment-emergent AEs, PK parameters, maximal antiviral effects.
Notes	The authors were contacted on VIROPHARMA all bias domains, mortality, SAE, SVR24. mean age, male:female, number of participants, final publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described

Chandra 2006a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with incomplete data was not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	Unclear risk	It was unclear how the trial was funded
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

COMMAND-1 2015a1

Methods	Randomised clinical phase IIb trial
Participants	395 participants **Sex:** 262 men, 133 women **Mean age:** 50.8 years **Countries:** North and Central America, Australia, North Africa, and Europe. **Inclusion criteria:** treatment-naive, aged 18–70 years who had chronic HCV genotype 1 or 4 infection. Compensated cirrhotic, infected with HCV genotype 1, and HCV genotype 4, were each capped at 10% of randomised participants. Cirrhosis was confirmed by biopsy at any time prior to randomisation. For non-cirrhotic participants, a liver biopsy must have been obtained within 24 months prior to randomisation. Additional inclusion criteria included HCV RNA ≥ 100,000 IU/mL and ALT levels < 5×ULN. **Exclusion criteria:** history or evidence of hepatic decompensation, prior exposure to any agent with potential anti-HCV activity, co-infection with HBV or HIV, or evidence of chronic liver disease other than HCV.
Interventions	Initally the trial was randomised into 3 groups (2 experimental groups, and 1 control group). After week 12, the participants who received a protocol-defined response, were re-randomised to placebo or additional 12 weeks of therapy. The participants without a protocol-defined response were treated with placebo and co-intervention. **Experimental group:** oral 20 mg of daclatasvir once a day for 12 weeks (after week 12, the participants with a protocol-defined response were re-randomised). **Experimental group:** oral 60 mg of daclatasvir once a day for 12 weeks (after week 12, the participants with a protocol-defined response were re-randomised). **Control group:** placebo. **Co-intervention:** peg-IFN α-2a administered subcutaneously at a dose of 180 mg per week and twice a day RBV dosed orally according to body weight (< 75 kg, 1000 mg daily; > 75 kg, 1200 mg daily). After week 24, all participants received standard care (peg-IFN-α-2a and RBV)
Outcomes	Safety assessment, efficacy assessment

COMMAND-1 2015a1 *(Continued)*

Notes	We emailedWe emailed Hezode and colleagues on 21 April 2016 for additional information on sequence generation, missing data, additional data, death but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	The trial used interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants were only blinded until week 24
Blinding of outcome assessment (detection bias) All outcomes	High risk	The sponsors, who performed the analyses, were only blinded until week 12
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

COMMAND-1 2015a2

Methods	For characteristics see COMMAND-1 2015a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	The trial used interactive voice-response system

COMMAND-1 2015a2 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants were only blinded until week 24
Blinding of outcome assessment (detection bias) All outcomes	High risk	The sponsors, who performed the analyses, were only blinded until week 12
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

CONCERTO-1 2015

Methods	Randomised phase III clinical trial
Participants	188 participants **Inclusion criteria:** HCV genotype 1 infection, treatment-naive male and female participants aged 20–70 years with documented chronic genotype 1 HCV infection and plasma HCV RNA P5.0 log10 IU/mL at screening. **Exclusion criteria:** liver cirrhosis, hepatic failure, any other liver disease of non-HCV etiology and co-infection with HIV-1, HIV-2, hepatitis B, or non-genotype 1 HCV.
Interventions	**Experimental group:** simeprevir 100 mg once a day plus peg-IFNa-2a/RBV for 12 weeks followed by response-guided therapy with peg-IFNa-2a/RBV alone for 12 or 36 weeks. **Control group:** placebo with peg-IFNa-2a/RBV for 12 weeks followed by peg-IFNa-2a/RBV for 36 weeks. Peg-IFNα-2a (Pegasys®, Chugai, Japan) was administered as a subcutaneous injection (180 µg once weekly) and RBV (Copegus®, Chugai) as oral tablets (600-1000 mg total daily dose, depending on body weight). **Co-intervention:** peg-IFN (subcutaneously at 180 µg/week) and RBV orally twice daily dosed according to body weight.
Outcomes	HCV RNA, safety assessment, ALT/AST elevations.
Notes	We emailedWe emailed Hayashi and colleagues on 21 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

CONCERTO-1 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed (NCT01292239)
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Cooper 2009

Methods	Randomised clinical trial
Participants	34 participants **Sex:** 21 men, 10 women (analysed only) **Mean age:** 42.9 years (analysed only) **Inclusion criteria:** treatment-naive genotype 1-infected male or female participants between 18 and 60 years of age with a BMI 633 kg/m2 were recruited. Baseline plasma HCV RNA greater than 100,000 IU/mL, ALT values < 5 times the ULN and a Metavir liver fibrosis stage between 0 and 3 were required. **Exclusion criteria:** none specified.
Interventions	**Experimental group:** VCH-759 doses (400 mg three times a day, 800 mg twice a day and 800 mg three times a day). VCH-759 was supplied as an oral solution formulation in individual 120 mL clear glass bottles. The oral solution was reconstituted by combining the appropriate VCH-759 powder-in-bottle dose in a 30% polyethylene glycol 400/15% Solutol HS15 aqueous reconstitution vehicle (20 mL for the 400 mg dose and 40 mL for the 800 mg dose). **Control group:** placebo. **Co-intervention:** none.
Outcomes	Absolute change in plasma HCV RNA levels between baseline to nadir, blood samples for evaluation of the plasma HCV RNA viral load, blood samples for NS5B polymerase, the complete PK profile.
Notes	We contacted the trial authors on 26 February 2016 by email ccooper@ottawahospital.on.ca about random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, did the trial account for the missing data, which group the the 2 participants dropped out from and was if there was a prepublished protocol, mortality, SAE, SVR24.

Cooper 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were above 5% drop outs and it was unclear how the trial handled participants with missing data
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The authors have declared that this study was funded by ViroChem Pharma Inc. JB, NC, RT, IB, ON, and LP are employees of ViroChem Pharma Inc. The other authors have also declared a relationship with the manufacturers of the drugs involved.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Dauphine 2015a1

Methods	Randomised, active-controlled phase IIb trial
Participants	**Sex:** 260 men, 157 women **Mean age:** 48 years **Inclusion criteria:** eligible participants were treatment-naive adults aged > 18 years with chronic HCV genotype 1 or 4 infection and HCV RNA above 50,000 IU/mL. Participants had to have evidence of chronic hepatitis C, documented by liver biopsy obtained within 24 months before randomisation. **Exclusion criteria:** participants with cirrhosis or incomplete/transition to cirrhosis (Knodell, Metavir, or Batts and Ludwig ≥ 3 or Ishak modified HAI ≥ 4); BMI < 18 or ≥ 36 kg/m2, other forms of liver disease; HIV infection; HCC; severe cardiac disease; severe depression or other psychiatric disease; renal disease; uncontrolled seizure disorders; severe retinopathy; haemoglobin < 12 g/dL for women or < 13 g/dL for men; neutrophil count < 90 cells/nL; serum creatinine > 1.5 times the ULN.
Interventions	Participants were randomised (2:2:2:2:1) to 1 of 5 treatment arms **Experimental group 1:** ritonavir boosted danoprevir (danoprevir/r) 200/100 mg twice a day for 24 weeks

Dauphine 2015a1 *(Continued)*

	Experimental group 2: ritonavir boosted danoprevir (danoprevir/r) 100/100 mg twice a day for 24 weeks **Experimental group 3:** ritonavir boosted danoprevir (danoprevir/r) 50/100 mg twice a day for 24 weeks **Experimental group 4:** ritonavir boosted danoprevir (danoprevir/r) 100/100 mg twice a day for 12 weeks or 24 weeks (participants achieving undetectable HCV RNA from Weeks 2 to 10 (eRVR2) stopped treatment at Week 12) **Control group:** participants in Arm E with detectable HCV RNA at Week 12 had the option to roll over to treatment with danoprevir/r 200/100 mg twice a day **Co-intervention:** peg-IFN α-2a (40KD) 180 lg/week and RBV 1000 mg/day (bodyweight < 75 kg) or 1200 mg/day (bodyweight ≥ 75 kg)
Outcomes	Proportion of participants with SVR24, with SAE, AEs, mortality.
Notes	Experimental group 1 vs Control.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were above 5% dropouts and it was unclear how the trial handled the missing participants
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported on: NCT01220947
Vested-interest bias	High risk	The trial was funded by F. Hoffmann-La Roche Ltd
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Dauphine 2015a2

Methods	For characteristics see Dauphine 2015a2
Participants	

Dauphine 2015a2 *(Continued)*

Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were above 5% dropouts and it was unclear how the trial handled the missing participants
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported on: NCT01220947
Vested-interest bias	High risk	The trial was funded by F. Hoffmann-La Roche Ltd
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Dauphine 2015a3

Methods	For characteristics see Dauphine 2015a2
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated randomisation

Dauphine 2015a3 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were above 5 % drop outs and it was unclear how the trial handLed the missing participants
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported on: NCT01220947
Vested-interest bias	High risk	the trial was funded by F. Hoffmann-La Roche Ltd. Support
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Dauphine 2015a4

Methods	For characteristics see Dauphine 2015a2
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unblinded

Dauphine 2015a4 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were above 5 % drop outs and it was unclear how the trial handLed the missing participants
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported on: NCT01220947
Vested-interest bias	High risk	The trial was funded by F. Hoffmann-La Roche Ltd
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

De Bruijne 2010a1

Methods	Randomised clinical trial
Participants	41 participants **Sex:** 31 men, 9 women **Mean age:** 48.8 years **Inclusion criteria:** 18-65 years with BMI of 18-40 kg/m2, HCV genotype 1 (any subtype), and HCV RNA level > 1 105 copies/mL (or equivalent international units). Chronic hepatitis C participants were naive, nonresponders or relapsers to previous IFN-based treatment. Relapse was defined as undetectable HCV RNA upon completion of a previous IFN-based treatment, but positive HCV RNA during follow-up. Nonresponse was defined as positive HCV RNA at the end of a previous IFN-based treatment or < 2-log decline in HCV RNA levels at 12 weeks and discontinued treatment. **Exclusion criteria:** key exclusion criteria included decompensated liver disease, findings consistent with Child-Pugh class B or C liver cirrhosis, and co-infection with HIV or HBV.
Interventions	**Experimental group:** participants received either 800 mg narlaprevir 3 times daily or 400 mg narlaprevir as an oral suspension in combination with for 7 days in the first period and for 14 days in the second period. **Control group:** placebo. **Co-intervention:** 200 mg ritonavir in cohort 3 and 4, a wash-out period after 1 week of treatment, 1.5 lg/kg/week peg-IFN-α-2b (in period 2) and standard care for 24 weeks after period 2.
Outcomes	Safety assessment, pharmacokinetic assessment, viral assessments.
Notes	Cohort 1 and 3 each included 10 participants naive to HCV treatment; cohorts 2 and 4 each included 10 HCV treatment-experienced participants. We report here the treatment-naive participants We contacted the trial authors on 26 February 2016 by email h.w.reesink@amc.nl about allocation concealment, how the blinding was maintained and who performed the outcome assessment; number of deaths, SAE, which group was the missing participants randomised to.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code

De Bruijne 2010a1 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant dropped out
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01081158) and the outcomes stated in the protocol were reported on
Vested-interest bias	High risk	Sponsored by Schering-Plough and designed by Schering-Plough employees and HW Reesink
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias.

De Bruijne 2010a2

Methods	For characteristics see De Bruijne 2010a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded and but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.

De Bruijne 2010a2 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant dropped out
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01081158) and the outcomes stated in the protocol are reported on
Vested-interest bias	High risk	Sponsored by Schering-Plough and designed by Schering-Plough employees and HW Reesink
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of other bias.

Detishin 2011

Methods	Randomised clinical trial
Participants	18 participants (only number of experimental group) **Country**: Moldova **Inclusion criteria**: healthy, treatment-naive or experienced HCV genotype 1 participants.
Interventions	**Experimental group:** oral 400 mg or 600 mg of ACH-1625 in fasted state for 5 days, or 600 mg of ACH-1625 once daily following a medium-fat meal for 5 days. **Control group:** placebo.
Outcomes	PK, safety, tolerability, effects on viral kinetics.
Notes	It was unclear whether the included participants included healthy participants, or healthy HCV genotype 1 participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being placebo blinded, but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being placebo blinded, but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described

Detishin 2011 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Several authors were sponsored by Achillion Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Dore 2015a1

Methods	Randomised clinical trial
Participants	152 adult participants **Sex:** 96 men, 55 women (analysed) **Mean age:** 47.9 years **Countries:** USA, Australia, Canada, Denmark, France, and Italy. **Inclusion criteria:** men and women aged 18–70 years, with chronic HCV genotype 2 or 3 infection and no prior exposure to HCV therapeutic agents including DAA, IFN preparations, or RBV. Participants were stratified by HCV genotype (2 or 3) before randomisation. Plasma HCV RNA levels at screening were required to be ≥100,000 IU/mL. Liver disease staging was conducted by liver biopsy within 2 years of screening (biopsies confirming cirrhosis), or by FibroScan (Echosens, Paris, France) within 1 year of screening (14.6 kPa was considered consistent with cirrhosis); participants with compensated cirrhosis were capped at approximately 10% of the study population. Women of childbearing potential and men who were sexually active partners of women of childbearing potential were required to use 2 forms of contraception, including at least 1 barrier method. **Exclusion criteria:** history or evidence of HCC, decompensated cirrhosis, or chronic liver disease other than hepatitis C; history of cancer within 5 years of enrolment; chronic HBV or HIV infection; presence of any other medical, psychiatric, and/or social reason that would render the patient inappropriate for study participation; gastrointestinal disease or surgical procedure that may impact absorption of the study drug; medical conditions prohibiting use of peg-α-2a or RBV, based on their respective product labels; or a history of hypersensitivity to compounds related to NS5A inhibitors. Exclusionary laboratory parameters included ALT level of 5 or more times the ULN; total bilirubin level of ≥ 2 mg/dL; international normalizsed ratio of ≥ 1.7; albumin level of ≤ 3.5 g/dL; haemoglobin level of ≤ 12 g/dL (for women) or ≤ 13 g/dL (for men); absolute neutrophil count of ≤ 1.5 109 cells/L (1.2 109 cells/L for black participants); platelet count of ≤ 90 109 cells/L; creatinine clearance of ≤ 50 mL/min; a fetoprotein level > 100 ng/mL; and corrected QT interval (QTcF) > 450 ms (for men) or > 470 ms (for women). Prohibited concomitant medications included inducers or strong or moderate inhibitors of CYP3A4; P-glycoprotein substrates with a narrow therapeutic index; strong P-glycoprotein inhibitors; nonstudy medications with known or potential anti- HCV activity; or any prescription or herbal product not prescribed for the treatment of a specific clinical condition. Doses of concomitant medications were required to be stable for 4 weeks or longer before the first dose of study drug.
Interventions	**Experimental group:** oral 60 mg of daclatasvir for 12 or 16 weeks. **Control group:** placebo for 24 weeks. **Co-intervention:** all participants received antiviral combination therapy with peg-α-2a 180 mg weekly, RBV 400 mg twice daily (800 mg/day).
Outcomes	Virological response, safety assessment.
Notes	NCT01257204

Dore 2015a1 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants were only blinded during treatment period
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study sponsor, who performed the analyses, were only blinded for the first 16 weeks
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	High risk	The trial changed the secondary outcomes
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Dore 2015a2

Methods	For characteristics see Dore 2015a2
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Interactive voice-response system

Dore 2015a2 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants were only blinded during treatment period
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study sponsor, who performed the analyses, were only blinded for the first 16 weeks
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	High risk	The trial changed the secondary outcomes
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

DRAGON 2014a1

Methods	Multicenter, randomised, open-label, parallel-group comparison trial (ClinicalTrials.gov number, NCT00996476)
Participants	93 were randomised to treatment groups, of whom 92 received at least 1 dose of the study drug **Mean age:** 54 years **Sex:** 43 men, 49 women **Inclusion criteria:** eligible participants were treatment-naive, chronically infected with genotype 1 HCV, aged 20–70 years and had plasma levels of HCV RNA > 5.0 log 10 IU/mL at screening **Exclusion criteria:** 1. presence of liver cirrhosis or hepatic failure, or other liver disease 2. infection/co-infection with HIV-1, HIV-2, hepatitis B or nongenotype 1 HCV 3. malignant tumor within 5 years prior to study 4. HCC 5. meeting conditions that required caution with peg-IFN α-2a or RBV treatment 6. any clinically significant disease 7. organ transplant 8. defined laboratory abnormalities during screening.
Interventions	Eligible participants were randomised to 1 of 5 treatment groups in a 2:1:2:1:1 ratio. **Experimental group 1**: simeprevir 50 mg once a day for 12 weeks. **Experimental group 2:** simeprevir 50 mg once a day for 24 weeks. **Experimental group 3:** simeprevir 100 mg once a day for 12 weeks. **Experimental group 4:** simeprevir 100 mg once a day for 24 weeks. NOTE: In these 4 groups, at week 24, participants either stopped or continued treatment with peg-IFN α-2a/RBV up to week 48, according to response-guided therapy criteria (stop treatment if plasma HCV RNA \1.4 log10 IU/mL at week 4 and undetectable at weeks 12, 16 and 20, otherwise continuing peg-IFN α-2a/RBV to week 48). In the PR48 group, criteria were not applied; participants received peg-IFNα-2a/RBV for 48 weeks. **Control group:** peg-IFN α-2a/RBV for additional 24 weeks (48 weeks PR treatment in total).

DRAGON 2014a1 *(Continued)*

	Co-intervention: peg-IFN α-2a/RBV for 24 weeks.
Outcomes	Proportion of participants with undetectable plasma HCV RNA 24 weeks after the end of treatment (SVR24), with SAE, AEs, mortality
Notes	According to predefined virologic stopping rules, participants in the simeprevir groups discontinued simeprevir and continued peg-IFN α-2a/RBV if viral breakthrough occurred during the first 24 weeks, and stopped all treatment if the decrease in plasma HCV RNA from baseline to week 12 was < 2 log10 IU/mL, or plasma HCV RNA level at week 24 was > = 1.2 log10 IU/mL. In this review SVR24 rates in the experimental group were analysed only from participants who did not continue treatment after 24 weeks. This is Group 1 vs control. We emailed Hayashi and colleagues on 21 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants dropped out
Selective reporting (reporting bias)	Low risk	The outcomes stated in the protocol were reported on
Vested-interest bias	High risk	Janssen Pharmaceutical KK
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

DRAGON 2014a2

Methods	For characteristics see DRAGON 2014a1
Participants	
Interventions	

DRAGON 2014a2 *(Continued)*

Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants dropped out
Selective reporting (reporting bias)	Low risk	The outcomes stated in the protocol were reported on
Vested-interest bias	High risk	Janssen Pharmaceutical K.K
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

DRAGON 2014a3

Methods	For characteristics see DRAGON 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

DRAGON 2014a3 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants dropped out
Selective reporting (reporting bias)	Low risk	The outcomes stated in the protocol were reported on
Vested-interest bias	High risk	Janssen Pharmaceutical KK
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

DRAGON 2014a4

Methods	For characteristics see DRAGON 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study

DRAGON 2014a4 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants dropped out
Selective reporting (reporting bias)	Low risk	The outcomes stated in the protocol were reported on
Vested-interest bias	High risk	Janssen Pharmaceutical KK
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Erhardt 2009

Methods	Randomised clinical trial
Participants	96 adult men **Sex:** 96 men **Mean age:** 44.6 years **Country:** Germany, Spain, and France **Inclusion criteria:** chronic HCV genotype 1 with minimal to mild liver fibrosis (Ishak score or Metavir grade < 2, confirmed by liver biopsy within the past 24 months) and HCV RNA viral load > 100.000 IU/mL at screening. No restriction was on the basis of prior IFN treatment experience. **Exclusion criteria:** laboratory measurements, HIV, HBV, any other additional cause for chronic liver disease, concurrent disease requiring treatment, any use of co-medication, treatment with IFN and/or RBV within 6 months prior to screening and use of any investigational drug 30 days prior to screening or 5 periods of drug plasma half life.
Interventions	Trial was divided into 8 cohorts and randomised in these cohorts. **Experimental group:** oral 10, 20, 40, 60, 80, 100, 150, 200, 300, 450 mg BILB-1941 three times a day for 4 days, plus a morning dose on 5th day. **Control group:** placebo.
Outcomes	Antiviral response, pharmacokinetics, safety assessment.
Notes	We emailed Erhardt and colleagues on 20 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed

Erhardt 2009 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Boehringer-Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Feld 2014

Methods	Multicenter, randomised, double-blind, placebo-controlled, parallel-design trial (SAPPHIRE-I) (NCT01716585)
Participants	631 participants **Location:** USA, Europe and Australia **Inclusion criteria:** age 18-70 years, chronic hepatitis C infection, genotype 1, HCV RNA level > 10,000 IU/mL, treatment-naive, no evidence of liver cirrhosis, women had to be post-menopausal for at least 2 years or surgically sterile or practicing specific forms of birth control. **Exclusion criteria:** hepatitis B or HIV co-infection, positive screen for drugs or alcohol, significant sensitivity to any drug, use of contraindicated medications within 2 weeks of dosing, certain predefined abnormal laboratory tests. **Group A:** 473 participants Sex: 217 men, 256 women Mean age, years (range): 49.4(18.0-70.0) Race, n(%): white: 428(90.5), black: 26(5.5), other: 19(4.0) Fibrosis score ≥ 2, n(%): 110(23.3), IL28B CC genotype, n(%): 144(30.4), HCV genotype, n(%): 1a: 322(68.1), 1b: 151(31.9) **Group B:** 158 participants Sex: 73 men, 85 women Mean age, years (range): 51.2(21.0-70.0) Race, n(%): white: 144(91.1), black: 8(5.1), other: 6(3.8) Fibrosis score ≥ 2, n(%): 42(26.6), IL28B CC genotype, n(%): 50(31.6), HCV genotype, n(%): 1a: 105(66.5), 1b: 53(33.5).
Interventions	**Experimental group:** ABT-450 orally at once-daily dose of 150 mg with ritonavir 100 mg once daily and ombitasvir orally 25 mg once daily for 12 weeks. Dasabuvir orally at a dose of 250 mg twice daily for 12 weeks.

Feld 2014 *(Continued)*

	Control group: matching placebos for 12 weeks, followed by an open-label period of 12 weeks' administration of the active treatment. **Co-interventions:** weight-based oral RBV 1000 to 1200 mg in 2 divided doses (1000 mg daily if body weight was < 75 kg, and 1200 mg daily if body weight was ≥ 75 kg).
Outcomes	**Primary outcomes:** percentage of participants achieving SVR 12 weeks after treatment. Safety of ABT-450/r/ombitasvir and dasabuvir co-administered with RBV for 12 weeks. **Secondary outcomes:** percentage of participants achieving RVR. Percentage of participants achieving end of treatment response. Percentage of participants with ALT normalisation at end of treatment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated schedules
Allocation concealment (selection bias)	Low risk	All participants assigned a unique participant number through the use of interactive response system in order to receive a unique study drug bottle/kit numbers and a unique randomisation number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebos were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All data were blinded to participants, study personnel, and sponsor. An independent data and safety monitoring committee reviewed safety data.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for withdrawal and discontinuation were clearly stated.
Selective reporting (reporting bias)	Low risk	A protocol was published before randomisation and all pre-specified outcomes were reported on.
Vested-interest bias	High risk	The sponsor (AbbVie) was directly involved in trial design, data analysis, drafting the manuscript and publication.
Other bias	Low risk	Seems free of other potential sources of bias.

Feld 2015

Methods	Randomised clinical trial
Participants	701 adult participants **Sex:** 442 men, 298 women (including genotype 5 participants) **Mean age:** 53.8 years (including genotype 5 participants)

Feld 2015 *(Continued)*

	Inclusion criteria: chronic infection with HCV genotype 1, 2, 4, or 6, willing and able to provide written informed consent, HCV RNA ≥ 10^4 IU/mL at screening, classification as treatment-naive or treatment-experienced. **Exclusion criteria:** current or prior history of clinically-significant illness (other than HCV) or any other major medical disorder that may interfere with treatment, assessment, or compliance with the protocol; individuals currently under evaluation for a potentially clinically-significant illness (other than HCV) are also excluded, screening ECG with clinically significant abnormalities, laboratory results outside of acceptable ranges at screening, prior exposure to sofosbuvir or other nucleotide analogue HCV NS5B inhibitor or any HCV NS5A inhibitor, infection with HBV or HIV.
Interventions	**Experimental group:** 400 mg of sofosbuvir and 100 mg of velpatasvir administered orally once daily for 12 weeks. **Control group:** placebo.
Outcomes	SVR12, SAE, AE, viral resistance.
Notes	Participants in the placebo group were eligible for deferred treatment with 12 weeks of sofosbuvir–velpatasvir. Genotype 5 participants were not eligible for randomisation. We contacted the trial authors on health-related quality of life (HRQoL), allocation sequence generation, if they reported their SVR24 anywhere, at email jordan.feld@uhn.ca.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	An interactive web response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was described as double-blind (participant, caregiver, investigator, outcomes assessor), and the placebo was described in the protocol
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was described as double-blind (participant, caregiver, investigator, outcomes assessor), and the placebo was described in the protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants had missing data
Selective reporting (reporting bias)	High risk	The trial did not report SVR24 as stated as a secondary objective in the protocol (NCT02201940 and supplementary material at NEJM.org)
Vested-interest bias	High risk	"The study was designed and conducted by the sponsor (Gilead Sciences) in collaboration with the principal investigators."
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

FISSION 2013

Methods	Randomised, open label, active-control study
Participants	527 participants were randomised and 499 participants were treated **Sex:** 327 men, 172 women **Mean age:** 48 years **Inclusion criteria:** eligible participants were treatment-naive adults aged 18 years or older with chronic hepatitis C genotype 2 or 3 infection and HCV RNA above 10,000 IU/mL. Participants with Childs A cirrhosis were included. **Exclusion criteria:** BMI < 18 kg/m2; positive HbS-Ab, positive HbC-Ag, positive immunoglobulin-M antibody, positive anti-HIV antibody, history of other liver disease, current evidence of psychiatric illness, immunologic disorder, haemoglobinopathy, pulmonary disease (including pneumonia or pneumonitis), cardiac disease, seizure disorder or anticonvulsant use, poorly controlled diabetes, cancer, or history of malignancy, clinical signs and symptoms of acute pancreatitis with elevated lipase, clinically significant ECG findings at screening, history of major organ transplantation with an existing functional graft, active substance abuse, history of uncontrolled thyroid disease, haemoglobin < 11 g/dL for women or < 12 g/dL for men; neutrophil count < 1500 cells/nL, serum creatinine > 1.5 times the ULN, ALT or AST ≥ 10 x ULN, albumin ≤ 3.2 g/dL, total bilirubin 1.5 x ULN (except participants with Gilbert's syndrome).
Interventions	**Experimental group 1:** oral sofosbuvir 400 mg once daily for 12 weeks. **Control group:** peg-IFN α-2a subcutaneous once weekly 180 µg for 24 weeks. **Co-intervention:** RBV 1000 mg/day (bodyweight < 75 kg) or 1200 mg/day (bodyweight ≥ 75 kg) for 12 or 24 weeks.
Outcomes	Proportion of participants with undetctable HCV RNA-level at week 2 and week 4 under treatment, with SVR12, with SAE, AEs, mortality.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Centralised system
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how the trial handled participants with missing data

FISSION 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported on
Vested-interest bias	Unclear risk	The sponsor (Gilead) collected the data, monitored the conduct of the study, and performed the statistical analysis
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Flamm 2013

Methods	Parallel group, double-blind, placebo-controlled, randomised trial
Participants	201 participants (134 in experimental group, 67 in control group) **Sex:** 141 men (70%), 60 women (30%) **Race:** 20 black (10%), 181 non-black (90%) **Cirrhosis, n(%):** 32(16%) Location**:** USA **Inclusion criteria:** chronic hepatitis C infection genotype 1 HCV RNA ≥ 10,000 IU/mL, demonstrated responsiveness to IFN (minimum duration of therapy 12 weeks); non-response defined as a decrease in HCV RNA of at least 2 $\log_{10}$ IU/mL by week 12, but with detectable HCV RNA during the therapy period; relapse defined as an undetectable HCV RNA at end of treatment, but without subsequent attainment of SVR. A liver biopsy with histology consistent with chronic hepatitis C, age ≥ 18 years, weight between 40-125 kg, signed informed consent, acceptable method of contraception for the participant and participant's partner(s) for at least 2 week before day 1 and continue until at least 6 months after treatment termination **Exclusion criteria:** hepatitis B infection, HIV infection, other causes of liver disease, decompensated liver disease, uncontrolled diabetes mellitus, a severe psychiatric disorder, active substance abuse, active or suspected malignancy, or a history of malignancy within last 5 years, pregnant or nursing women, severe AE during prior treatment, seizure disorder, cerebrovascular diseases, cardiovascular disease, autoimmune diseases, prior organ transplantation, haemoglobinopathies, coagulopathies, abnormal levels of serum bilirubin, albumin, and creatinine, haemoglobin < 120 g/L (women) and < 130 g/L (men), neutrophil count < 1500/mm^3, platelet count < 100,000/mm^3.
Interventions	**Experimental group:** oral boceprevir 800 mg thrice daily for 44 weeks, beginning at week 5. **Control group:** placebo for 44 weeks, beginning at week 5. **Co-interventions:** peg-IFNα-2a 180 µg subcutaneously once weekly and oral weight-base RBV 1000 to 1200 mg daily in divided doses for 48 weeks.
Outcomes	**Primary outcome:** SVR 24 weeks post-therapy.
Notes	We emailed Flamm and colleagues on 20 April 2016 for additional information (on: random sequence generation; method of allocation concealment; description of blinding procedure; blinding of outcome assessors; potential number and reasons for dropouts; pre-defined outcomes; sponsorship and its role; type of SAE) but reply not received yet. -

Risk of bias

Flamm 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated that trial was randomised, but the method of sequence generation was not described
Allocation concealment (selection bias)	Low risk	The trial used an interactive voice-response system.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Trial defined as double-blind and placebo was used in the control group. However, method of blinding was not adequately described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not mentioned if the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	High risk	The trial authors changed their primary outcomes according to the protocol (NCT00845065)
Vested-interest bias	High risk	The trial was funded by Schering-Plough
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias.

Forestier 2007

Methods	Randomised clinical trial
Participants	20 participants. **Sex:** 12 men, 8 women **Mean age:** 45.5 years **Inclusion criteria:** men and women of non-childbearing potential aged between 18 and 60 years. Participants satisfied the following criteria for inclusion in the study: genotype 1 chronic hepatitis C; had not received any prior therapy for hepatitis C, including approved treatments or participation in studies of investigational treatments; HCV RNA level > 1×10^5 IU/mL ALT concentration < 4.0 times the ULN, no clinically significant deviations from the normal range for haematology or clinical chemistry values; willing to refrain from the concomitant use of herbal dietary supplements or vitamins during the study drug-dosing period; and willing to initiate standard-of-care treatment (peg-IFNα and RBV) at the conclusion of the study drug-dosing period. **Exclusion criteria:** contraindications to peg-IFNα-2a or RBV; decompensated liver disease; alcohol-related cirrhosis or primary biliary cirrhosis; positive screening for hepatitis B surface antigen or HIV co-infection; donation of blood (500 mL) within 60 days before the first dose of study drug; concurrent antiviral therapy (except for antiviral agents approved for treatment of herpes viruses) within 3 months preceding study entry; regular treatment with nontopical medications or with topical medications with known systemic absorption within 4 weeks before study drug administration (with the exception of oestrogen replacement therapy for women); regular consumption of more than 24 units of alcoholic drinks per week or more than 8 cups of coffee per day; history of drug abuse within 6 months of study entry; history of methadone use within 3 months of study entry; positive urine screen for drugs of

Forestier 2007 *(Continued)*

	abuse; participation in an investigational drug study within 90 days before study drug administration or participation in more than 2 drug studies in the last 12 months (excluding the present study); or participation in a prior clinical study of telaprevir unless it was documented that the participant had been randomised to placebo treatment. Participants were also excluded if they had a history of any illness that, in the opinion of the investigator or the participant's general practitioner, may have confounded the results of the study or posed an additional risk in administering study drug to the participant. This included but was not limited to a history of relevant drug or food allergies; cardiovascular or central nervous system disease; clinically significant illness; or mental illness that may have affected compliance with study requirements.
Interventions	**Experimental group:** telaprevir was given as 750 mg oral doses every 8 h. Telaprevir alone every 8 h orally for 14 days (8 participants); or telaprevir every 8 h orally for 14 days and peg-IFNα-2a once weekly for 2 weeks (8 participants) **Control group:** placebo every 8 h orally for 14 days and peg-IFNα-2a via subcutaneous injection once weekly for 2 weeks (4 participants) **Co-intervention:** peg-IFNα-2a was given as weekly 180 mg subcutaneous injections After completing study drug dosing, participants were offered the opportunity to begin standard therapy for chronic hepatitis C (180 g/week peg-IFNα-2a and 1000 or 1200 mg/day RBV, depending on body weight
Outcomes	Safety assessment, pharmacokinetic assessment, viral assessments
Notes	We contacted trial authors for additional information on allocation concealment, blinding of participants and personal, blinding of outcome assessment, SVR data protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random-number generator
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was placebo-controlled for telaprevir; peg-IFNα-2a treatment was open-label. Investigators and participants were blinded to HCV RNA results during the study drug-dosing period
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear how (and if there was any blinding at all) the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Vested-interest bias	High risk	Supported by Vertex Pharmaceuticals Incorporated
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Forestier 2011a1

Methods	Randomised clinical trial
Participants	50 participants **Sex:** 40 men, 10 women **Mean age:** 48 years **Inclusion criteria:** men and women between 18 and 65 years of age with a history of chronic HCV genotype 1 infection and detectable plasma HCV RNA (> 1 104 IU/mL) at the study screening visit. Additional enrolment criteria included a BMI between 18 and 30, minimum body weight of 45 kg, and a liver biopsy or non-invasive procedure (liver scan) within the previous 2 years showing no evidence of cirrhosis. In addition, participants in Part A were required to have no history of prior therapy with IFN-based regimens; participants in Part B were required to have had failed previous IFN-alfa and RBV-based therapy as defined above. **Exclusion criteria:** participants were excluded from the study if they met any of the following criteria: decompensated liver disease; impaired liver function; clinical or histopathologic evidence of cirrhosis; history of non-hepatitis C chronic liver disease; positive screening for hepatitis B surface antigen or HIV infection; history of active malignancy within the preceding 5 years; history of clinically significant cardiovascular or cerebrovascular disease; treatment with peg-IFN-α and RBV (Part A) or treatment with peg-IFN-α and RBV within 3 months before screening (Part B); treatment with growth factors within 3 months before screening; history of drug abuse within the previous year; regular consumption of more than 1 glass of alcohol per day for women or 2 glasses of alcohol per day for men; participation in an investigational drug study within 3 months of screening or any prior participation in a study of an experimental HCV therapy; and selected laboratory abnormalities, including serum ALT > 5 times the upper limit of the reference range, creatinine clearance < 30 mL/min, or total bilirubin P26 lmol/L. Pregnant or lactating women, women of childbearing potential, and male partners of pregnant or lactating women were excluded from enrolment. Additionally, anyone who, in the opinion of the investigator, was not a suitable candidate for enrolment or was unlikely to comply with the requirements of the study was also excluded from enrolment.
Interventions	**Experimental group:** **Group 1:** danoprevir was administered orally in soft gelatin capsule form in total daily doses of 200, 300, 400 and 600 mg in treatment-naive participants. **Group 2:** a single dose level of danoprevir (600 mg daily) was explored in a cohort of non-responders (NR) **Control intervention:** placebo
Outcomes	Safety assessments, pharmacokinetics, viral kinetics
Notes	4 cohorts of 10 participants each were randomised (8:2) to treatment with danoprevir or placebo equivalent. In Part A, treatment-naive (Cohorts 1–5) were permitted but not required to begin standard of care (SOC) treatment with peg-IFN-α/RBV anytime after 24 h following the last dose of the study drug. 3 treatment-naive participants in the 200 mg every-12-h cohort who were mis-dosed at a single study site were excluded from the efficacy analysis. We sent an email was sent to Forestier and colleagues on 20 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using an interactive voice-response system that assigned a participant identification number that corresponded to treatment assignment (danoprevir or placebo) according to the randomisation code.

Forestier 2011a1 *(Continued)*

Allocation concealment (selection bias)	Low risk	Participants were randomised using an interactive voice-response system that assigned a participant identification number that corresponded to treatment assignment (danoprevir or placebo) according to the randomisation code.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded, but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants excluded. Clearly stated reason
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Vested-interest bias	High risk	The study was sponsored by InterMune, Inc. and Roche
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Forestier 2011a2

Methods	For characteristics see Forestier 2011a2
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using an interactive voice-response system that assigned a participant identification number that corresponded to treatment assignment (danoprevir or placebo) according to the randomisation code.
Allocation concealment (selection bias)	Low risk	Participants were randomised using an interactive voice-response system that assigned a participant identification number that corresponded to treatment assignment (danoprevir or placebo) according to the randomisation code.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded, but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias)	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.

Forestier 2011a2 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants excluded. Clearly stated reason
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Vested-interest bias	High risk	The study was sponsored by InterMune, Inc. and Roche
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Forestier 2011b

Methods	Randomised clinical trial
Participants	59 participants **Sex:** 46 men, 13 women **Mean age:** 45.8 years **Inclusion criteria:** genotype 1 chronic HCV infection with detectable plasma HCV RNA levels (> 1 x 10^4 IU/mL), no previous treatment for HCV infection, an age of 18–65 years, a BMI (defined as the weight in kilograms divided by the square of the height in meters) of 18–30, and no evidence of cirrhosis during the previous 2 years in a liver biopsy or noninvasive procedure (e.g. elastography). **Exclusion criteria:** decompensated liver disease; impaired liver function; clinical or histopathologic evidence of cirrhosis; history of non–hepatitis C chronic liver disease; screening positive for hepatitis B surface antigen or HIV infection; history of active malignancy during the preceding 5 years; history of clinically significant cardiovascular or cerebrovascular disease; previous treatment with peg-IFN-a and RBV; treatment with growth factors within 3 months before screening; history of drug use within the previous year; regular consumption of > 1 glass of alcohol per day for women or > 2 glasses of alcohol per day for men; participation in an investigational drug study within 3 months before screening or any prior participation in a study of an experimental HCV therapy; and selected laboratory abnormalities, including ALT level .5 times the upper limit of the reference range, creatinine clearance < 30 mL/min, or total bilirubin level >26 mmol/L. Pregnant or lactating women, women of childbearing potential, and male partners of pregnant or lactating women were excluded from enrolment. In addition, anyone who, in the opinion of the investigator, was not a suitable candidate for enrolment or was unlikely to comply with the requirements of the study was also excluded from enrolment.
Interventions	**Experimental group:** danoprevir was administered orally in soft gelatin capsule form in the following dose regimens: 100 mg 3 times daily, 200 mg 3 times daily, 300 mg 3 times daily, 400 mg twice daily, 600 mg twice daily, and 900 mg twice daily. The 5 lowest dose cohorts consisted of 10 participants randomised (8:2) to receive treatment with danoprevir or placebo equivalent. The highest dose cohort consisted of 9 participants randomised (7:2) to receive treatment with danoprevir or placebo equivalent. 6 dose cohorts (400 mg, 600 mg, and 900 mg twice daily and 100 mg, 200 mg, and 300 mg 3 times daily). Participants also received peg-IFN a-2a (180 lg once weekly) and RBV (1000–1200 mg/day) on day 0 and 15. **Control group:** placebo plus peg-IFN a-2a (180 lg once weekly) and RBV (1000–1200 mg/day) **Co-intervention:** peg-IFN-a 2 a(180 lg once weekly) and RBV (1000–1200 mg/day)
Outcomes	Safety assessments and viral kinetics

Forestier 2011b *(Continued)*

Notes	We sent an email to Forestier and colleagues on 20 April 2016 for additional information (missing blinding during assessment of allocation concealment, missing SVR and mortality data - is it investigated) but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised using an interactive voice-response system, which assigned a participant identification number corresponding with treatment assignment (danoprevir or placebo), according to the randomisation code.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant withdrew because of a family emergency after 1 dose of study drug, and 1 participant withdrew because of poor venous access after 4 doses of study drug. A third participant (administered 100 mg 3 times daily) missed 6 danoprevir doses during days 12–14 but was included in efficacy analyses, because 0.90% of danoprevir doses were administered
Selective reporting (reporting bias)	Unclear risk	No protocol was found
Vested-interest bias	High risk	This study was supported by InterMune and Roche.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Forns 2014

Methods	Randomised, multicenter, double-blind, parallel-group, placebo-controlled, phase III clinical trial (PROMISE)(NCT01281839)
Participants	393 participants (260 in experimental group and 133 in control group) **Sex:** 258 men, 135 women **Mean age:** 52 years (range 20-70 years) **Location:** Europe, North America, Australia, and New Zealand. **Inclusion criteria:** age ≥ 18 years. Confirmed chronic genotype 1 HCV infection. Screening plasma HCV RNA levels > 10,000 IU/mL. Treatment-experienced participants who had relapsed after 24 weeks or more of IFN-based therapy (undetectable HCV RNA at end of treatment or within 2 months after end of treatment, with documented relapse within 1 year after therapy). A liver biopsy specimen obtained within 3 years of screening showing histology consistent with chronic HCV infection (participants with

Forns 2014 *(Continued)*

	bridging fibrosis (F3) or cirrhosis (F4) were eligible if they had an ultrasound performed within 6 months before screening (or between the screening and baseline visit) with no findings suspicious for HCC) **Exclusion criteria:** hepatic decompensation. Non–HCV-related liver disease. HBV, HIV, or non-genotype 1 HCV co-infection. Defined laboratory abnormalities: platelets < 90,000/mm^3, white blood cell count < 3000/µL, haemoglobin level < 12 g/dL for women and < 13 g/dL for men, creatinine level > 1.5 mg/dL, ALT and/or AST level > 10 times the upper limit and normal, total serum bilirubin level 1.5 times or more the ULN, and α-fetoprotein level > 50 ng/mL in participants with cirrhosis. Any other active disease. Pregnant women or planning pregnancy were excluded
Interventions	**Experimental group:** oral simeprevir 150 mg once daily for 12 weeks **Control group:** placebo for 12 weeks **Co-interventions:** **Experimental group**: peg-IFN α-2a 180 µg subcutaneously once weekly for 24 weeks (if HCV RNA < 25 IU/mL at week 4 and undetectable at week 12) or 48 weeks if not meeting these criteria. Oral weight-based RBV 1000 to 1200 mg daily for 24 weeks (if HCV RNA < 25 IU/mL at week 4 and undetectable at week 12) or 48 weeks if not meeting these criteria **Control group**: peg-IFN α-2a 180 µg subcutaneously once weekly for 48 weeks. Oral weight-based RBV 1000 to 1200 mg daily for 48 weeks
Outcomes	**Primary outcome:** proportion of participants achieving SVR 12 weeks after planned end of treatment (SVR12) **Secondary outcomes:** comparison of other virologic response rates at other time points. Rate of RVR. Proportion of simeprevir-treated participants meeting response-guided treatment criteria to complete treatment at week 24. Incidence of viral breakthrough. Incidence of on-treatment failure. Incidence of viral relapse. Incidence of AEs. Laboratory abnormalities. Quality-of-life measures.
Notes	We sent an email to Forns and colleagues on 20 April 2016 for the following additional information. Reply received on 27 April 2016 with data on baseline number of participants with elevated AST/ALT and randomisation details.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information given
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated that "participants, study personnel, and the sponsor were blinded to the treatment assignments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated that "participants, study personnel, and the sponsor were blinded to the treatment assignments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The proportion of patients who discontinued simeprevir/placebo intake early was 3.5% and 72.2% in the simeprevir/PR and placebo/PR groups, respectively. The main reason for discontinuation was meeting the week 4 virologic stopping rule for simeprevir or placebo in both arms, with a large proportion of patients in the placebo group (69.9%) stopping placebo at week 4. The proportion of patients who completed PR treatment was 93.5% in the

Forns 2014 *(Continued)*

		simeprevir/PR group (24 or 48 weeks) and 72.2% in the placebo/PR group (48 weeks)"
Selective reporting (reporting bias)	Low risk	A protocol was published before randomisation. Outcomes specified in the protocol are similar, but not completely equal to the ones stated in the article. Not all outcomes stated in the protocol were reported in the article, but results of all outcomes were reported and available on www.ClinicalTrials.gov.
Vested-interest bias	High risk	Trial sponsored by Janssen
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias.

Foster 2011a1

Methods	Multicenter randomised clinical trial
Participants	52 participants **Sex:** 35 men, 17 women **Mean age:** 44 years **Countries:** France, UK, Italy, and Sweden **Inclusion criteria:** 18–65 years; chronic infection with either genotype 2 or genotype 3 HCV (serum HCV RNA > 10,000 IU/mL); absolute neutrophil count > 1500 mm^3 and platelet count > 100,000 mm^3; no prior treatment for HCV **Exclusion criteria:** relevant concomitant medical condition; decompensated liver disease or cirrhosis, or other significant liver disease; HIV or HBV co-infection; peg-IFN or RBV contraindication; a history of alcohol or illicit drug use; pregnancy/breast feeding
Interventions	The participants were randomised according to genotype 2 and 3 **Experimental group 1:** oral 750 mg telaprevir every 8th hour for 2 weeks **Experimental group 2:** oral 750 mg telaprevir every 8th hour + peg-IFN-α-2a 180 µg once weekly plus RBV 400 mg twice daily for 2 weeks **Control group:** telaprevir placebo (every 8 h) plus peg-IFN-α-2a 180 µg once weekly plus RBV 400 mg twice daily for 2 weeks **Co-intervention:** The peg-IFN-α-2a and RBV were a co-intervention between control group and experimental group 2 during treatment period, and all participants received peg-IFN-α-2a 180 g once weekly plus RBV 400 mg twice daily for 24 weeks after treatment.
Outcomes	Viral kinetics, efficacy and safety assessment
Notes	We emailed Foster and colleagues on 21 April 2016 for additional information (randomisation, blinding, death, missing data) but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described (central randomisation system)

Foster 2011a1 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The monotherapy group was not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% percent dropped out (7 participants)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	Unclear risk	The trial was funded by Janssen Pharmaceuticals and Vertex Pharmaceuticals)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Foster 2011a2

Methods	For characteristics see Foster 2011a1	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described (central randomisation system)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The monotherapy group was not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Foster 2011a2 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% percent dropped out (7 participants)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	The trial was funded by Janssen Pharmaceuticals and Vertex Pharmaceuticals)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Foster 2015a1

Methods	Randomised clinical trial
Participants	558 adult participants **Sex:** 374 men, 178 women **Mean age:** 49.5 years **Inclusion criteria:** chronic hepatitis C genotype 3 who were treatment-naive or treatment-experienced, and were required to have liver imaging within 6 months of baseline/Day 1; adults with cirrhosis to exclude HCC , women of childbearing potential (as defined in Appendix 4 must have a negative serum pregnancy test at screening and a negative urine pregnancy test on Baseline/Day 1 prior to randomisation, male participants and female participants of childbearing potential who engage in heterosexual intercourse had to agree to use protocol-specified method(s) of contraception, lactating women had to agree to discontinue nursing before the study drug was administered, participant had to be of generally good health, with the exception of chronic HCV infection, as determined by the Investigator, participant had to be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments **Exclusion criteria:** current or prior history of clinically-significant illness (other than HCV that may interfere with treatment, assessment or compliance with the protocol, screening ECG with clinically significant abnormalities, laboratory results outside of acceptable ranges at screening, pregnant or nursing female or male with pregnant female partner, chronic liver disease of a non-HCV aetiology (e.g. haemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency, cholangitis), infection with HBV or HIV
Interventions	**Experimental group:** 100 mg of velpatasvir once a day and 400 mg of sofosbuvir once a day for 12 weeks **Control group:** 400 mg of sofosbuvir plus RBV 1000 or 1200 mg (weight-based) both for 24 weeks
Outcomes	SVR12, SAE, death, viral resistance
Notes	We could only use data reported at 12 weeks meaning no data were available. We contacted the trial authors for additional information on allocation sequence generation, how many had incomplete outcome data at 12 weeks, SAE, death, health-related quality of life) at 12 weeks at g.r.foster@qmul.ac.uk on 21 April 2016 but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement

Foster 2015a1 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	An Interactive Web Response System was used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were above 5% dropouts and it was unclear how the trial handled missing participants. It was unclear how many dropouts there were at 12 weeks.
Selective reporting (reporting bias)	Unclear risk	SVR 24 was not reported as described in the prepublished protocol NCT02201953 and supplementary material at NEJM.org
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Gilead Sciences)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Foster 2015a2

Methods	For characteristics see Foster 2015a2
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	An Interactive Web Response System was used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as open-label

Foster 2015a2 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Described as open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants dropped out
Selective reporting (reporting bias)	High risk	SVR 24 was not reported as described in the prepublished protocol (NCT02220998 and supplementary material at NEJM.org)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Gilead Sciences)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Fried 2013

Methods	Phase IIb, double-blind, placebo-controlled, parallel-group trial (PILLAR)(NCT00882908)
Participants	386 participants **Sex:** 213 men, 173 women **Location:** 13 countries in North America, Europe, and Asia-Pacific regions **Inclusion criteria:** adult participants with chronic hepatitis C, plasma HCV RNA > 100,000 IU/mL, genotype 1, treatment-naive, eligible to be treated with peg-IFN-based regimens according to standard criteria **Exclusion criteria:** cirrhosis on liver biopsy (required within 24 months of enrolment), HIV or HBV co-infection, platelet count < 90,000/mm3, haemoglobin< 12 g/dL for women and 13 g/dL for men **Group 1:** 78 participants Sex: 40 men (51.3%), 38 women (48.7%) Median age: 47 years (range 19-66) **Group 2:** 75 participants Sex: 47 men(62,7%), 28 women (37.3%) Median age: 46 years (range 18-67) **Group 3:** 77 participants Sex: 43 men (55.8%), 34 women (44.2%) Median age: 47 years (range 18-69) **Group 4:** 79 participants

Fried 2013 *(Continued)*

	Sex: 44 men (55.7%), 35 women (44.3%) Median age: 47 years (range 19-69) **Group 5:** 77 participants Sex: 39 men (50.6%), 38 women (49.4%) Median age: 45 years (range 21-67).
Interventions	**Experimental group:** **Group 1:** oral simeprevir 75 mg once daily for 12 weeks, followed by placebo for 12 weeks. **Group 2:** oral simeprevir 75 mg once daily for 24 weeks. **Group 3:** oral simeprevir 150 mg once daily for 12 weeks, followed by placebo for 12 weeks. **Group 4:** oral simeprevir 75 mg once daily for 24 weeks. **Control group:** **Group 5:** matched placebo for 24 weeks. **Co-intervention for all groups:** peg-IFN-α-2a 180 µg subcutaneously once weekly. Oral RBV 1000-1200 mg daily.
Outcomes	**Primary outcome:** proportion of participants with HCV RNA< 25 IU/mL undetectable at week 72 (SVR W72). **Secondary outcome:** SVR at 12 and 24 weeks after planned end of treatment (SVR12 and SVR24, respectively). Adverse events. Quality-of-life measures. Assessment of HCV-NS3 sequence in participants not achieving SVR. Assessment of simeprevir pharmacokinetics. The influence of interleukin-28 (IL28)B genotype on efficacy was explored in a subset of participants for whom genomic DNA was available. Influence of IL28B genotype on treatment efficacy.
Notes	We emailed Fried and colleagues on 21 April 2016 for additional information (baseline number of participants with elevated AST/ALT and method of sequence generation but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned in equal proportions, using a centralised, interactive voice/web response randomisation system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated that "participants and personnel were blinded to the experimental intervention. A simeprevir-matched placebo was used."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as blinded. An external physician monitored individual HCV RNA results and informed investigators regarding protocol-directed treatment discontinuation
Incomplete outcome data (attrition bias)	Low risk	Withdrawals reported with reasons given. Treatment discontinuation rate 7.5%

Fried 2013 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	A protocol was published before randomisation began and all outcome results were reported adequately (NCT00882908)
Vested-interest bias	Unclear risk	This study was funded by Janssen Research & Development, LLC. Editorial support was provided by Dr Bethan Hahn, on behalf of Complete Medical Communications, funded by Janssen Research & Development, LLC.
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Fundamental 2014a1

Methods	Prospective, double-blind, multinational, randomised, placebo controlled phase II trial (CDE-B025A2210; ClinicalTrials.gov NCT01183169) conducted between 30 August 2010 and 9 May 2013
Participants	459 eligible participants **Sex:** 278 men, 181 women **Mean age:** 50.6 years **Countries:** Europe, North America, Asia-Pacific region **Inclusion criteria:** 9-69 years with chronic hepatitis C genotype 1 infection and HCV RNA > = 1000 IU/mL and had failed to respond to or had relapse after prior P/R therapy; all participants had to have a liver biopsy within 3 years or transient elastography within 6 months of enrolment. Participants with compensated cirrhosis were eligible. **Exclusion criteria:** nongenotype 1 infection, presence or history of hepatic decompensation and haematological abnormalities, and recent treatment with any anti-HCV drug, concomitant treatment with known substrates or inhibitors of cytochrome P450 3A, P-gp, OATPs, MRP2 or BSEP was not permitted within 2 weeks of study entry. 459 participants randomised, 77% white, 25% compensated cirrhosis/transition to cirrhosis, 57% prior P/R-non responders, 79% genotype IL28B 457 treated.
Interventions	Participants were randomised (1:1:1:1) **Experimental group 1:** alisporivir 600 mg once a day for 48 weeks. **Experimental group 2:** alisporivir 800 mg once a day for 48 weeks. **Experimental group 3:** alisporivir 400 mg twice a day for 48 weeks. **Control group:** placebo for 48 weeks. **Co-intervention:** peg-IFN-α-2a 180 lg/week plus RBV 1000 or 1200 mg/day based on body weight for 48 weeks.
Outcomes	eEVR (weeks 12 on treatment), SVR12, SVR24, all-cause mortality, AEs.
Notes	Following a partial clinical hold imposed by FDA, alisporivir/placebo was discontinued in all participants; at that time, all active participants had received at least 31 weeks of triple therapy out of a total of 48 weeks. Analysis group 1 vs control.

Fundamental 2014a1 *(Continued)*

	In the placebo arm, 57% of participants were switched in a blinded manner to alisporivir plus P/R after Week 16 due to failure to achieve the efficacy criterion (HCV RNA < limit of quantification) at Week 12. We could therefore not use the results from this trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was only missing data for 2 participants
Selective reporting (reporting bias)	High risk	The secondary outcomes were changed from the original secondary outcomes
Vested-interest bias	High risk	The study was funded by Novartis
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Fundamental 2014a2

Methods	For characteristics see Fundamental 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Fundamental 2014a2 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was only missing data for 2 participants
Selective reporting (reporting bias)	High risk	The secondary outcomes were changed from the original secondary outcomes
Vested-interest bias	High risk	The study was funded by Novartis.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Fundamental 2014a3

Methods	For characteristics see Fundamental 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Fundamental 2014a3 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	There was only missing data for 2 participants
Selective reporting (reporting bias)	High risk	The secondary outcomes were changed from the original secondary outcomes
Vested-interest bias	High risk	The study was funded by Novartis
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Gane 2008

Methods	Randomised clinical trial
Participants	25 adult participants **Country:** New Zealand **Inclusion criteria:** Non responders for RBV and IFN, infected with genotype 2 or 3. All participants were non-cirrhotics, and treated with at least 12 weeks of IFN prior to randomisation.
Interventions	**Experimental group:** 1500 mg R7128 twice daily for 28 days. **Control group:** placebo twice daily for 28 days. **Co-intervention:** 180µg peg-IFN and 1000-1200mg RBV.
Outcomes	HCV RNA, SAE, AEs
Notes	We emailed Gane and colleagues on 21 April 2016 for additional information regarding randomisation, blinding, missing data, death, additional data, separate data from Genotype 2 and 3.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were missing data from 7 participants (above 5%)

Gane 2008 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	A clinicalTrials.gov number was found, but it was unclear which outcome was supposed to be assessed in each part of the trial
Vested-interest bias	High risk	The main author was consulting in pharmaceutical companies
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Gane 2010

Methods	Randomised clinical trial
Participants	71 participants **Sex:** 54 men, 17 women **Mean age:** 47.6 years **Inclusion criteria:** treatment-naive and treatment-experienced adults aged 18–65 years, who were chronically infected with HCV genotype 1 but did not have cirrhosis, and who had a minimum HCV RNA of 10^5 IU/mL. Participants were required to have normal renal and hepatic function and no clinically significant comorbidities. **Exclusion criteria:** co-infection with hepatitis B or HIV, concurrent medical or psychiatric disorder (or history of such), history of any neoplastic disease, history of clinically significant cardiovascular or cerebrovascular disease, use of growth factors, or anticipated use or need for significant concomitant medical treatment.
Interventions	**Experimental group:** Arm B: 500 mg RG7128 twice daily and 100 mg danoprevir every 8 h (treatment-naive) Arm C1: 500 mg RG7128 twice daily and 200 mg danoprevir every 8 h (treatment-naive) Arm C2 1000 mg RG7128 twice daily and 100 mg danoprevir every 8 h (treatment-naive) Arm D: 1000 mg RG7128 twice daily and 200 mg danoprevir every 8 h (treatment-naive) Arm E: 1000 mg RG7128 twice daily and 600 mg danoprevir twice a day (non-null responders) Arm F: 1000 mg RG7128 twice daily and 900 mg danoprevir twice a day (null responders) Arm G: 1000 mg RG7128 twice daily and 900 mg danoprevir twice a day (treatment-naive) **Control group:** placebo RG7128 and Placebo Danoprevir **Co-intervention:** standard of care treatment (180 µg/week peg-IFN α-2a, and RBV at 1000 mg/day for participants weighing < 75 kg or 1200 mg/day for those weighing ≥ 75 kg)
Outcomes	Safety, pharmacokinetics, antiviral activity
Notes	We emailed Gane and colleagues on 06 June 2016 for additional information on SVR24 but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement

Gane 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	The random allocation sequence was computer-generated
Allocation concealment (selection bias)	Low risk	Randomly assigned by interactive voice or web response system to active treatment or placebo
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators, personnel at the study centre, and participants were masked to treatment allocation. Study drugs and placebo were identical in colour, size, shape, and taste but "(...) apart from patients in cohort F, who were unmasked after the last assessment was completed"
Blinding of outcome assessment (detection bias) All outcomes	High risk	The pharmacist who prepared the doses, personnel involved in pharmacokinetic sample analyses, statisticians who prepared data summaries, and the clinical pharmacologists who reviewed the data before deciding to initiate dosing in the next cohort were not masked to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was under 5% dropouts (only 2 dropouts)
Selective reporting (reporting bias)	Low risk	The outcomes stated in the protocol were reported on (NCT00801255)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Gane 2011

Methods	Randomised clinical trial
Participants	30 adult participants **Sex:** 21 men, 9 women **Mean age:** 44.5 years **Countries:** New Zealand, France, Poland **Inclusion criteria:** 18-65 years and with chronic treatment-naive hepatitis C genotype 1 infection, an HCV RNA level > $x10^5$ IU/mL, a BMI between 18 and 35 kg/m2 and without evidence of liver cirrhosis on a liver biopsy or non-invasive procedure (e.g. Fibroscan) obtained within the preceding 24 months were eligible for the trial. **Exclusion criteria:** decompensated liver disease; impaired liver function (indicated by a history of ascites, hepatic encephalopathy, HCC or bleeding oesophageal varices); chronic liver disease attributed to a cause other than HCV; or serological evidence of HBV or HIV infection. Increased risk of anaemia; a clinically significant medical condition such as cardiovascular or cerebrovascular disease, chronic pulmonary disease, poorly controlled thyroid function, diabetes mellitus requiring medication, ophthalmic disorders related to diabetes or hypertension, or diseases associated with alterations in immune function; or a history of clinically significant psychiatric disease, a history of excessive alcohol consumption (defined as more than 2 standard drinks per day within the previous 3 months), or a history of drug abuse within the last year, pregnant and lactating women and male partners of pregnant women, any recent use or anticipated need for drugs, herbal preparations or nutrients known to inhibit or induce CYP enzymes, or were substrates of CYP3A or CYP2C9 with a narrow therapeutic index (including oral contraceptives, steroids, antacids, H-2 blockers or proton-pump inhibitors). Systemic im-

Gane 2011 *(Continued)*

	munosuppressive drugs, cytotoxic or chemotherapeutic agents, radiation therapy, oral or inhaled corticosteroids, or topical class 1 and 2 steroids. ALT level > 5 times the ULN, creatinine clearance < 50 mL/min, haemoglobin < 120 g/L (if female) or < 130 g/L (if male), an absolute neutrophil count < 1.5 10^9/L, platelet count < 100 x 10^9/L, or serum albumin level < 35 g/L
Interventions	The study consisted of 3 cohorts. The randomisation was within each cohort. **Experimental group:** participants received 100 mg oral danoprevir twice a day, 200 mg oral danoprevir once a day, or 200 mg oral danoprevir twice a day for 15 days. **Control group:** placebo in same numbers as above. **Co-intervention:** both groups received equal amounts of ritonavir (100 mg) pr pill. subcutaneous peg-IFN α-2a (40KD) (Pegasys, Roche, Basel, Switzerland) 180 µg once weekly plus oral RBV 1000 mg/day (bodyweight < 75 kg) or 1200 mg/day (bodyweight > 75 kg). After the 15 days, both groups received peg-IFN α-2a (40KD) plus RBV for a total of 48 weeks.
Outcomes	Pharmacokinetic parameters (plasma concentration, AUC), HCV RNA level, safety assessment (laboratory test, AEs).
Notes	We emailed Gane and colleagues on 06 June 2016 for additional information on blinding, other outcomes, protocol but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation
Allocation concealment (selection bias)	Low risk	Randomisation was managed through a centralised interactive voice and web response system through a 3rd party
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as "partially" double-blinded but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as "partially" double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts
Selective reporting (reporting bias)	High risk	The protocol stated "Virological response in prior null-responders" as a secondary outcome. This outcome was not assessed in any study
Vested-interest bias	High risk	The trial was sponsored by F. Hoffmann-La Roche Ltd
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Gane 2015

Methods	Randomised clinical trial
Participants	30 adults with chronic hepatitis C infection **Sex:** 17 men, 13 women **Mean age:** 45 years **Countries:** New Zealand and USA
Interventions	**Experimental group 1:** 12 participants randomised to 50 mg ACH-3102 (odalasavir) and 400 mg sofosbuvir once a day for 8 weeks **Control group 1:** 6 participants randomised to observation for 8 weeks. **Experimental group 2:** 6 participants randomised to 50 mg ACH-3102 (odalasavir) and 400 mg sofosbuvir once a day for 6 weeks **Control group 2:** 6 participants randomised to observation for 6 weeks.
Outcomes	SVR, SAE.
Notes	Abstract only. After 4 weeks of treatment, group 1 (both experimental and control group) were merged, and received active treatment, therefore data can not be used after week 4. We emailed Gane and colleagues on 21 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Observation group" not placebo controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Sponsored by Achillion Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Gardner 2014a

Methods	Randomised clinical trial
Participants	16 participants **Sex:** 14 men, 1 women (analysed) **Mean age:** 53 years **Countries:** USA and Puerto Rico **Inclusion criteria:** treatment-naive participants men and women 18-70 years of age with HCV genotype 1 or 4 infection for at least 6 months and HCV RNA ≥ 1,00,000 IU/mL at screening. Eligible participants had no evidence of cirrhosis documented by liver biopsy within 3 years. Fertile men or women were required to use 2 forms of effective contraception between them and their partner during treatment and for 24 weeks afterwards **Exclusion criteria:** co-infection with hepatitis B, HIV, clinically significant chronic liver disease, conditions consistent with decompensated liver disease, drug or alcohol abuse, significant ECG findings, history of suicide attempt, major depression or current severe or poorly controlled psychiatric disorder. Abnormal haematological and biochemical parameters that excluded participation were: Neutrophil count (< 1500 cells/mm3 ((or < 1250 cells/mm3 for African American/Black participants)); haemoglobin (< 11 g/dL in women or 12 g/dL in men); creatinine > 1.5 x ULN (ULN); ALT, AST, or alkaline phosphatase > 5 x ULN; total bilirubin > 2.0 x ULN ((except in participants with Gilbert's) syndrome; albumin < 3.0 g/dL and platelet count < 90,000/mm3. Participants were excluded if they received herbal/natural remedies with anti-HCV activity within 30 days of the baseline visit. The use of systemic antineoplastic or immunomodulatory treatments within 6 months of the baseline visit excluded participation and was not allowed during this study. The use of growth factors was not allowed during this study. In the absence of clinical drug interaction study data, medications that modulate stomach acid and known inhibitors or inducers of the cytochrome P450 3A enzyme and P-glycoprotein transporter systems were prohibited.
Interventions	**Experimental group:** oral 60 mg of GSK2336805 for 28 days. **Control group:** placebo for 28 days. **Co-intervention:** peg-IFN α-2a (180 µg per week) and RBV (1000–1200 mg daily) from day 2 and for 27 days in total.
Outcomes	Safety assessment, HCV RNA, pharmacokinetics.
Notes	NCT01439373. The trial had 2 parts. Part 1: 1-day therapy with GSK2336805 versus placebo. Part 2: 27 days of GSK2336805 versus placebo with RBV and peg-IFN as co-intervention. We emailed Gardner and colleagues on 21 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed

Gardner 2014a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out (1 person)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol (NCT01439373) were assessed
Vested-interest bias	High risk	GlaxoSmithKline, LLC
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

GlaxoSmithKline 2014

Methods	Randomised clinical trial
Participants	37 adult participants (18-60 years) chronically infected with HCV (genotype 1 (1a or 1b), genotype 2 or genotype 4.
Interventions	**Experimental group:** oral GSK2878175 10 mg, 30 mg or 60 mg for 2 days. **Control group:** placebo.
Outcomes	Safety, pharmacokinetics, HCV RNA.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being blinded but it was unclear how the blinding of outcome assessors was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 5% dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained

GlaxoSmithKline 2014 *(Continued)*

Vested-interest bias	High risk	The trial was sponsored by Glaxo Smith Kline
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Goldwater 2010

Methods	Randomised clinical trial
Participants	32 adult treatment-naive participants with HCV genotype1 **Country:** USA
Interventions	**Experimental group:** oral 150 mg, 300 mg, 450 mg of GS-9256 as a single dose. **Control group:** placebo.
Outcomes	HCV RNA, pharmacokinetics.
Notes	The trial also had groups with healthy volunteers.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being placebo blinded, but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being placebo blinded, but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Gilead Sciences
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

HALLMARK-DUAL 2014

Methods	Randomised clinical trial
Participants	307 adult participants **Sex:** 155 men, 152 women **Mean age:** 54.5 years **Countries:** Argentina, Australia, Austria, Canada, France, Germany, Ireland, Israel, Italy, Republic of Korea, Netherlands, New Zealand, Poland, Russian Federation, Spain, Taiwan, UK and USA. **Inclusion criteria:** aged at least 18 years with genotype 1b infection and HCV RNA of 10,000 IU/mL or greater who met inclusion criteria for 1 of 3 cohorts: treatment-naive, previous non-responder to peg-IFNα plus RBV (null or partial response), or ineligible for, intolerant of, or ineligible for and intolerant of peg-IFN α plus RBV (treatment-naive and treatment-experienced). Ineligible or intolerant (or both) participants included those with depression, anaemia or neutropenia, or compensated advanced fibrosis or cirrhosis (F3/F4) with thrombocytopaenia. Anaemia was defined as haemoglobin between 85 g/L and < 120 g/L (women) or < 130 g/L (men), neutropenia as absolute neutrophils between 0.5 x 10^9 cells per L and < 1.5 x 10^9 cells per L, and thrombocytopenia as platelets between 50 x 10^9 cells per L and < 90 x 10^9 cells per L, at screening or history of these conditions, while receiving peg-IFN α plus RBV, or both. **Exclusion criteria:** people with HIV, ascites, oesophageal varices, or other evidence of hepatic decompensation.
Interventions	**Experimental group:** oral 60 mg once daily of daclatasvir and oral 100 mg twice daily of asunaprevir for 24 weeks. **Control group:** placebo for 12 weeks.
Outcomes	HCV RNA (SVR), safety assessment.
Notes	Only participants in the treatment-naive group were randomised. The placebo group entered a new study after 12 weeks, therefore only data for the first 12 weeks could be used. We emailed Manns and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and personnel were blinded to treatment allocation until week 12, and we used data until week 12
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The sponsors, who performed the analyses, were blinded until week 12, and we used data until week 12
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The amount of drop-outs until week 12 were not described

HALLMARK-DUAL 2014 *(Continued)*

Selective reporting (reporting bias)	High risk	2 outcomes were added to the secondary outcomes in the protocol (NCT01581203)
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Han 2014

Methods	Randomised, placebo-controlled, parallel-group trial
Participants	107 participants **Ethnicity:** Korean **Race:** Asian **Country:** South Korea, India, Taiwan **Inclusion criteria:** chronic hepatitis C infection and genotype 1. Previous treatment failure (relapse, non-responders, and partial responders)
Interventions	**Experimental group:** boceprevir for 32 weeks, beginning at week 5. **Control group:** placebo for 44 weeks, beginning at week 5. **Co-interventions:** **Experimental group**: peg-IFN and RBV for 36 week (participants with detectable HCV RNA at week 8 received additional 12 weeks of treatment, in total 48 weeks). **Control group**: peg-IFN and RBV for 48 weeks.
Outcomes	Not specified
Notes	This trial was only available as an abstract of an interim-analysis. The co-interventions in both groups (experimental and control) were not completely equal - while all the participants in the control group received Peg-IFN + RBV for 48 weeks, the experimental group received a response-guided regimen which implied that some participants received shorter duration of treatment (36 weeks), while others received 48 weeks. The following Information is required: number of participants randomised per group; method of sequence generation; method of allocation concealment; description of blinding; number and reasons for withdrawal; pre-specified outcomes; sponsorship and its role No contact details of authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided

Han 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Use of placebo suggests blinding, but method of blinding was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided. No protocol available
Vested-interest bias	Unclear risk	It was uncertain how the trial was sponsored
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Hezode 2009

Methods	A phase IIb, randomised, partially double-blind, placebo-controlled, parallel-group trial (PROVE-2) (NCT00372385)
Participants	323 participants **Sex:** 192 men, 131 women **Country:** France, Germany, the UK, and Austria **Inclusion criteria:** age between 18 and 65 years. Chronic hepatitis C infection. HCV genotype 1. Detectable plasma HCV RNA levels. treatment-naive. No histologic evidence of cirrhosis within 2 years before study Day 1. Seronegative for hepatitis B surface antigen and HIV-1 and 2. Adequate double method of contraception. Negative pregnancy test for women. **Exclusion criteria:** any medical contraindication to peg-IFN α-2a or RBV therapy. Any other cause of significant liver disease in addition to hepatitis C. Diagnosed or suspected HCC. Alcohol/drug abuse or excessive use in the last 12 months. Participation in any investigational drug study within 90 days before drug administration. **Group 1:** 81 participants: (T12PR24) Sex: 54 men, 27 women Median age: 46 years (range 19-65) Race: 75 white (93%), 1 black (1%), 3 Asian (4%), 1 Hispanic (1%), 1 other (1%) HCV RNA ≥ 800,000 IU/mL, n(%): 73(90) Fibrosis, n(%): none or minimal: 35(43). Portal: 37(46). Bridging: 9(11). Cirrhosis: 0 HCV genotype, n(%): 1a: 31(38). 1b: 50(62). Intermediate: 0 **Group 2:** 82 participants (T12PR12) Sex: 49 men, 33 women

Hezode 2009 *(Continued)*

	Median age: 44 years (range 22-65) Race: 76 white (93%), 2 black (2%), 2 Asian (2%), 1 Hispanic (1%), 1 other (1%) HCV RNA ≥ 800,000 IU/mL, n(%): 67(82) Fibrosis, n(%): none or minimal: 30(37). Portal: 46(56). Bridging: 6(7). Cirrhosis: 0 HCV genotype, n(%): 1a: 37(45). 1b: 45(55). Intermediate: 0 **Group 3:** 78 participants (T12P12) Sex: 43 men, 55 women Median age: 45 years (range 20-64) Race: 77 white (99%), 1 black (1%), 0 Asian, 0 Hispanic, 0 other HCV RNA ≥800,000 IU/mL, n(%): 63(81) Fibrosis, n(%): none or minimal: 31(40). Portal: 43(55). Bridging: 3(4). Cirrhosis: 1(1) HCV genotype, n(%): 1a: 40(51). 1b: 38(49). Intermediate: 0 **Group 4:** 82 participants (PR48) Sex: 46 men, 36 women Median age: 45 years (range 18-64) Race: 76 white (93%), 2 black (2%), 4 Asian (5%), 0 Hispanic, 0 other HCV RNA ≥800,000 IU/mL, n(%): 68(83) Fibrosis, n(%): none or minimal: 28(34). Portal: 46(56). Bridging: 8(10). Cirrhosis: 0 HCV genotype, n(%): 1a: 35(43). 1b: 45(55). Intermediate: 2(2).
Interventions	**Experimental group:** 1, 2, and 3: oral telaprevir given as a single dose of 1250 mg on study day 1, followed by a dose of 750 mg every 8 h for 12 weeks. **Control group:** 4: placebo for 12 weeks. **Co-interventions:** 1: peg-IFN α-2a 180 µg subcutaneously once weekly plus oral weight-based RBV 1000 to 1200 mg in 2 divided daily doses for 24 weeks 2: peg-IFN α-2a 180 µg subcutaneously once weekly plus oral weight-based RBV 1000 to 1200 mg in 2 divided daily doses for 12 weeks 3: peg-IFN α-2a 180 µg subcutaneously once weekly for 12 weeks 4: peg-IFN α-2a 180 µg subcutaneously once weekly plus oral weight-based RBV 1000 to 1200 mg in 2 divided daily doses for 48 weeks.
Outcomes	**Primary outcome:** proportion of participants who achieved SVR at 24 weeks after end of treatment (HCV RNA undetectable (< 10 IU/mL) 24 weeks after completion of study treatment) **Secondary outcomes:** proportion of participants with undetectable HCV RNA at week 12 after end of treatment. Proportion of participants with undetectable HCV RNA at completion of study drug dosing.

Hezode 2009 *(Continued)*

	Number of participants with AEs. Number of participants with viral relapse. Maximum, minimum, and average plasma concentration of telaprevir
Notes	We emailedWe emailed Hezode and colleagues on 21 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Randomisation was performed through a central telephone-based system. No other information was provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Group 3 (T12P12) was not blinded. Other treatment groups were blinded to the interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for discontinuation were clearly reported on.
Selective reporting (reporting bias)	Low risk	Protocol was available and all pre-specified outcomes were reported on
Vested-interest bias	High risk	The sponsor (Vertex Pharmaceuticals) was directly involved in trial design and protocol development
Other bias	Low risk	The trial seems to be free of other potential sources of bias

Hinrichsen 2004

Methods	Randomised clinical trial
Participants	51 adult participants **Sex:** 41 men, 10 women **Mean age:** 47.8 years **Countries:** Germany, France, and Spain. **Inclusion criteria:** women or men aged 18 years or older with chronic genotype 1 HCV infection. The line probe assay was used to determine the genotype of the viral infection. A liver biopsy specimen showing changes consistent with chronic HCV infection had to have been performed within the previous 12 months. At screening, the HCV load had to be 50,000 copies/mL serum. **Exclusion criteria:** women were excluded if they were breast-feeding or at risk of pregnancy; men had to use an adequate form of contraception if their partner was of childbearing potential. They were not enrolled if there were other or additional reasons for chronic liver disease, including the presence of other hepatitis-causing viruses and/or a history of alcohol abuse within the previous 12 months and/or

Hinrichsen 2004 *(Continued)*

	evidence of Child's B or C liver disease at screening. No other antiviral or antimicrobial or investigational therapies were allowed during the study (screening, pretreatment, and treatment phases). Patients were excluded if, at screening, their baseline ALT/AST) plasma levels exceeded the ULN by more than 5-fold (5 times the ULN) or their total bilirubin or alkaline phosphatase levels were 1.5 times the ULN. Other exclusion criteria included co-infection with HIV, a platelet count 100,000/mm3, a white blood cell count 2000 cells/mm3, any clinically significant laboratory abnormalities, and a positive test result for illicit or nonprescription drugs.
Interventions	The trial was divided into 3 different cohorts, according to grade of liver disease (Ishak score, Metavir score). **Experimental group:** 2 days of oral 25 mg, 200 mg or 500 mg of BILN-2061 in participants with Ishak score 0-2. Oral 200 mg of BILN 2061 in participants with Ishak score 3-4. Oral 200 mg of BILN 2061 in participants with Ishak score 5-6. **Control group:** placebo.
Outcomes	Virologic efficacy, pharmacokinetics, safety assessment.
Notes	We emailedWe emailed Hinrichsen and colleagues on 21 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	0 participants dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained for all 3 stages, and the clinicalTrials.gov information was added after completion
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Hoeben 2015a1

Methods	Phase III, randomised, double-blind, placebo-controlled, parallel-group trial (TIGER)(NCT01725529)

Hoeben 2015a1 *(Continued)*

Participants	457 participants **Median age:** 48 years (range 18-68) **Sex:** 236 men, 221 women **Country:** China, Korea **Ethnicity (%):** Chinese (80.3%), Korean (19.7%) **HCV genotype (%):** 1a (1.1%), 1b (98.9%) **Inclusion criteria:** treatment-naive East Asian participants with chronic hepatitis C. A liver biopsy within 3 years prior to the screening visit (or between screening and day of randomisation) with histology consistent with chronic Hepatitis C virus (HCV) infection (presence of contraindications for a liver biopsy in participants who are otherwise deemed eligible for participation does not exclude the patient from participation). Genotype 1 HCV infection (confirmed at screening). Plasma HCV RNA of > 10,000 IU/mL at screening. Age between 18-70 years. **Exclusion criteria:** prior treatment with any approved or investigational drug for the treatment of hepatitis C. Co-infection with HBV or HIV.
Interventions	**Experimental group:** Group 1: Simeprevir 150 mg orally once daily for 12 weeks. Group 2: Simeprevir 100 mg orally once daily for 12 weeks. **Control group:** Group 3: matching placebo capsules taken orally with food once-daily for 48 weeks. **Co-interventions:** Group 1 and 2: peg-IFN α-2a µg once weekly administered as weekly subcutaneous injections of 0.5 mL for 24 or 48 weeks. RBV 1000 or 1200 mg/day (taken as 100 mg or 200 mg tablets) depending on body weight for 24 or 48 weeks (If body weight is < 75 kg the total daily dose of RBV will be 1000 mg, administered as 400 mg intake with food in the morning and 600 mg intake with food in the evening. If body weight is > or = 75 kg the total daily dose will be 1200 mg, administered as 2 x 600 mg per intake with food, morning and evening). Group 3: peg-IFN α-2a µg once weekly administered as weekly subcutaneous injections of 0.5 mL for 48 weeks. RBV 1000 or 1200 mg/day (taken as 100 mg or 200 mg tablets) depending on body weight for 48 weeks (If body weight is < 75 kg the total daily dose of RBV will be 1000 mg, administered as 400 mg intake with food in the morning and 600 mg intake with food in the evening. If body weight is ≥ 75 kg the total daily dose will be 1200 mg, administered as 2 x 600 mg per intake with food, morning and evening).
Outcomes	**Primary outcome measures:** percentage of participants with SVR 12 weeks after end of study drug treatment (participants considered to have achieved SVR12 if both conditions are met: 1. HCV RNA < 25 IU/mL or undetectable at end of treatment and; 2. HCV RNA is < 25 IU/mL or undetectable at 12 weeks after the planned end of study drug treatment). **Secondary outcome measures:** percentage of participants with SVR 24 weeks after end of study drug treatment (participants considered to have achieved SVR24 if both conditions are met: 1. HCV RNA < 25 IU/mL or undetectable at end of treatment; 2. HCV RNA < 25 IU/mL or undetectable at 24 weeks after the planned end of study drug treatment). Percentage of participants with SVR at week 72. Percentage of participants with on-treatment failure (refers to a participant with confirmed detectable HCV RNA at the end of treatment). Percentage of participants with viral breakthrough (defined as a confirmed increase of > 1 log10 IU/mL in HCV RNA level from the lowest level reached, or a confirmed HCV RNA level of > 100 IU/mL in participants whose HCV RNA levels had previously been below the limit of quantification (< 25 IU/mL detectable) or undetectable (< 25 IU/mL undetectable) while on study treatment). Percentage of participants with viral relapse (defined as undetectable HCV RNA at the actual end of treat-

Hoeben 2015a1 *(Continued)*

	ment and last HCV RNA measurement during follow-up ≥ 25 IU/mL). Percentage of participants with on-treatment normalisation of ALT level.
Notes	Abstract. Interim analysis. We emailedWe emailed Hoeben and colleagues on 21 April 2016 for additional information (on method of sequence generation and method of allocation concealment) but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A simeprevir-matched placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The protocol stated that outcomes assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for withdrawal were stated at www.ClinicalTrials.gov (NCT01725529)
Selective reporting (reporting bias)	Low risk	A protocol was published before randomisation began and all outcome results were reported adequately
Vested-interest bias	High risk	The trial was sponsored by a pharmaceutical company (Janssen)
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Hoeben 2015a2

Methods	For characteristics see Hoeben 2015a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Hoeben 2015a2 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A simeprevir-matched placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The protocol stated that outcomes assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for withdrawal were stated at www.ClinicalTrials.gov (NCT01725529)
Selective reporting (reporting bias)	Low risk	A protocol was published before randomisation began and all outcome results were reported adequately
Vested-interest bias	High risk	The trial was sponsored by a pharmaceutical company (Janssen)
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Hotho 2012

Methods	Randomised clinical trial
Participants	13 participants **Sex:** 12 men, 1 woman **Mean age:** 49 years **Countries:** Netherlands and USA. **Inclusion criteria:** chronic hepatitis C participants, both treatment-naive or treatment-experienced, aged 18-65 with a BMI 18-32. **Exclusion criteria:** decompensated liver disease, uncontrolled or active major systemic disease and co-infection with HIV or HBV. Participants with chronic stable haemophilia or on stable methadone substitution treatment.
Interventions	The trial was divided into single and multi ascending cohorts (only cohort 4, 5 and 11, 12 were HCV-infected participants) **Experimental group 1:** single ascending dose: 100 mg, 500 mg once daily, or 250 mg twice daily PHX1766 **Experimental group 2:** multi ascending dose: 400 mg twice daily, 800 mg twice daily PHX1766 **Control group:** placebo, only in the multi ascending dose
Outcomes	Pharmacokinetics, safety assessment, pharmacodynamics.

Hotho 2012 *(Continued)*

Notes	We emailed Hotho and colleagues on 21 April 2016 for additional information but reply not received yet. The trial also included healthy volunteers.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being placebo-controlled, but method was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being placebo-controlled, but method was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Phenomix Corporation
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Isakov 2016

Methods	Randomised clinical trial
Participants	Treatment-naive and treatment- experienced participants (prior treatment with PR for ≥ 12 weeks had failed) with chronic HCV genotype 1 infection.
Interventions	All participants initially received PR for 4 weeks. Participants randomised to control treatment then received PR for an additional 44 weeks. Treatment-naive participants randomised to triple therapy received boceprevir (800 mg 3 times daily) plus PR for 24 weeks and then further therapy according to treatment week 8 HCV RNA levels. Treatment-experienced participants received boceprevir plus PR for 32 wk and then further therapy according to treatment week 8 HCV RNA levels.
Outcomes	SVR defined as undetectable HCV RNA 24 weeks after completing all study therapy.
Notes	

Risk of bias

Isakov 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 5% missing data
Selective reporting (reporting bias)	Unclear risk	No protocol
Vested-interest bias	High risk	"Supported by Merck and Co., Inc. Kenilworth, NJ, US."; "Medical writing and editorial assistance were provided by Tim Ibbotson, Ph.D. of ApotheCom, Yardley,PA, United States."

Izumi 2014a1

Methods	Randomised clinical trial
Participants	42 adult participants **Sex:** 20 men, 22 women **Mean age:** 55 years **Country:** Japan **Inclusion criteria:** Japanese men and women 20-70 years of age chronically infected with HCV genotype 1 (HCV RNA > 10^5 IU/mL) who were treatment-naive (with alfa-2a or 2b/RBV or DAA), or those who were non-responders to previous therapy. Women of childbearing potential were required to use effective methods of contraception. **Exclusion criteria:** history of HCC, co-infection with HBV or HIV, other chronic liver disease, or evidence of hepatic decompensation. Liver cirrhosis, liver biopsy within 24 months, elevated ALT, bilirubin, albumin, decreased haemoglobin, white blood cells, neutrophil count, platelets, creatinine, participants exposed any investigational HCV therapeutic agent 4 weeks prior to dosing.
Interventions	**Experimental group:** oral 10 mg or 60 mg of daclatasvir once daily. **Control group:** placebo. **Co-intervention:** weight-based RBV twice daily, once weekly subcutaneous alfa-2a IFN. Participants receiving protocol-defined response were treated for 24 weeks. Participants not receiving protocol-defined response were treated for 48 weeks.

Izumi 2014a1 *(Continued)*

Outcomes	Efficacy assessment, safety assessment, virological response.
Notes	NCT01017575 - only data from the treatment-naive group could be used, since the non-responders couldn't be randomised to placebo. We emailed Izumi and colleagues on 21 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not described
Allocation concealment (selection bias)	Low risk	Central randomisation centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded after week 24
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded after week 24
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 person dropped out
Selective reporting (reporting bias)	High risk	The trial changed the primary outcomes
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Izumi 2014a2

Methods	For characteristics see Izumi 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Izumi 2014a2 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Central randomisation centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded after week 24
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded after week 24
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 person dropped out
Selective reporting (reporting bias)	High risk	The trial changed the primary outcomes
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Jacobson 2010

Methods	Randomised clinical trial
Participants	35 adult participants **Sex:** 18 men, 17 women **Mean age:** not reported **Country:** USA and Puerto Rico. **Inclusion criteria:** 18-65 years of age treatment-naive (no prior treatment with IFN-a +/- RBV regimens, discontinued IFN-a containing regimens after < 2 weeks of therapy due to tolerability issues were considered treatment-naive, HCV RNA > 100,000 IU/mL at screening, genotype 1, a diagnosis of chronic HCV infection for at least 6 months. **Exclusion criteria:** evidence of acute or chronic infection with HIV or HBV, exposure within the previous 3 months to an investigational anti-HCV agent, evidence of severe or decompensated liver disease, participants with liver disease unrelated to HCV infection.
Interventions	**Experimental group:** oral 200 mg, 300 mg, 500 mg twice daily for 4 weeks. **Control group:** placebo. **Co-intervention:** standard care as per investigator's discretion up to Week 48, then off-treatment up to Week 72 in open-label period. Standard of care included peg-IFN α-2a 180 µg subcutaneously once weekly starting from day 1 and RBV 1000 mg/day tablet orally in 2 divided doses for participants weighing ≤ 75 kg; 1200 mg/day orally in 2 divided doses for participants weighing > 75 kg.

Jacobson 2010 *(Continued)*

Outcomes	Plasma HCV, pharmacokinetics, ALT levels, safety assessment.
Notes	NCT00720434 We emailed Jacobson and colleagues on 21 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label after week 4
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label after week 4
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out (Jacobson 2010, described 2 dropping out)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	The trial was funded by Pfizer
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Jacobson 2014

Methods	A phase III, multicenter, randomised, double-blind, parallel-group trial (QUEST-1) (NCT01289782)
Participants	394 participants **Country:** Australia, Canada, Germany, Italy, Mexico, New Zealand, Puerto Rico, Romania, Russia, Spain, Ukraine, UK, and USA **Inclusion criteria:** age ≥ 18 years with chronic hepatitis C infection and HCV genotype 1. Screening HCV RNA level > 10,000 IU/mL, treatment-naive, an ultrasound performed within 6 months of enrolment showing no signs of HCC in participants with cirrhosis. **Exclusion criteria:** hepatic decompensation, any non-HCV-related liver disease, HIV or HBV co-infection, non-genotype 1 HCV infection, significant laboratory abnormalities, any other active disease, male or female participants who had, or were planning to conceive **Simeprevir group:** 264 participants:

Jacobson 2014 *(Continued)*

	Sex: 148 men, 116 women Median age: 48 years (range 39-54) Race: 227 white (86%), 27 black or African-American (10%), 5 Asian (2%) HCV genotype 1a: 147 (56%). HCV genotype1b: 117 (44%) Interleukin (IL) 28B genotype CC: 77 (29%). IL28B genotype CT: 150 (57%). IL28B genotype TT: 37(14) HCV RNA > 800,000 IU/mL, n(%): 218(83) **Placebo group:** 130 participants: Sex: 74 men, 56 women Median age: 48 years (range 36-54) Race: 122 white (94%), 4 black or African-American (3%), 3 Asian (2%) HCV genotype, n(%): 1a: 74(57). 1b: 56(43). IL28B genotype, n(%): CC: 37(28). CT: 76(58). TT: 17(13) METAVIR score, n(%): F0-F1: 50(38). F2: 40(31). F3: 23(18). F4: 17(13). HCV RNA > 800,000 IU/mL, n(%): 96(74)
Interventions	**Experimental group:** oral simeprevir 150 mg once daily for 12 weeks. **Control group:** oral placebo 150 mg once daily for 12 weeks. **Co-interventions:** Experimental group: peg-IFN alfa-2a 180 µg subcutaneously once weekly and oral weight-based RBV 1000-1200 mg in 2 divided daily doses for 24-48 weeks Control group: pegIFN α-2a 180 µg subcutaneously once weekly and oral weight-based RBV 1000-1200 mg in 2 divided daily doses (1000 mg if body weight < 75 kg; 1200 mg if body-weight ≥ 75 kg) for 48 weeks.
Outcomes	**Primary outcome:** proportion of participants achieving SVR12 (HCV RNA < 25 IU/mL undetectable at end of treatment and < 25 IU/mL detectable or undetectable 12 weeks after planned end of treatment) **Secondary outcomes:** comparison of SVR 24 weeks after planned end of treatment. Percentage of participants meeting criteria for response-guided therapy to complete treatment at week 24. Rapid virological response (HCV RNA < 25 IU/mL undetectable at week 4). On-treatment failure (detectable HCV RNA at end of treatment). Incidence of viral breakthrough (HCV RNA increase of more than 1 $\log_{10}$ from the lowest level noted or an HCV RNA ≥ 25 IU/mL during follow-up or at time of SVR assessments after achieving undetectable levels at end of treatment). Incidence of AEs. Incidence of laboratory abnormalities. Patient-reported symptoms and functioning. Effect of baseline characteristics on treatment response. Assessment of depression severity. Assessment of health status.
Notes	We emailed Jacobson and colleagues on 21 April 2016 for additional information (on blinding of outcomes assessors) but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated schedule prepared by or under the supervision of the sponsor was used

Jacobson 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation concealment was performed by "using an interactive voice-response system (IVRS) which assigned a unique code that dictated the treatment assignment and matching study drug kit for each patient". Randomisation codes were maintained within the IVRS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors stated that "patients, study personnel, and the sponsor were masked to the treatment group assignment", the blinding method was not adequately described. A matched placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although RNA levels were monitored by an unmasked independent external person who informed the sponsor of any required changes to treatment, the blinding method for other outcome assessors was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for discontinuation were clearly reported on
Selective reporting (reporting bias)	Low risk	Protocol is available. All pre-specified study outcomes were reported on
Vested-interest bias	High risk	The sponsor (Janssen Infectious Diseases-Diagnostics) was directly involved in trial design, analyses and interpretation of data, writing and reviewing the manuscript
Other bias	Low risk	The trial seems free of other potential sources of bias

JUMP-C 2013

Methods	Phase IIb, randomised, double-blind, parallel-group study in treatment-naive participants with HCV genotype 1 or 4 infection (ClinicalTrials.gov NCT01057667)
Participants	168 participants were randomised **Sex:** 118 men, 48 women **Mean age:** experimental group: 49.7 years/control group: 48.2 years **Countries:** 25 sites in the USA and Canada. **Inclusion criteria:** eligible participants were treatment-niıve adults 18-70 years of age with chronic hepatitis C of at least 6 months' duration, a serum HCV RNA titer of at least 50,000 IU/mL (COBAS AmpliPrep/ COBAS TaqMan HCV Test; lower limit of detection ¼ 15 IU/mL), and HCV genotype 1 or 4 infection were eligible for the study. Participants were required to have had a liver biopsy within the previous 24 months (36 months in participants with cirrhosis/bridging fibrosis). Participants with compensated cirrhosis (Child-Pugh grade A) or transition to cirrhosis were required to have had an abdominal ultrasound, computerised tomography scan, magnetic resonance imaging scan demonstrating the absence of evidence of HCC (within 2 months before randomisation), and a serum alpha-fetoprotein level < 100 ng/mL. **Exclusion criteria:** infection with hepatitis A or B viruses or HIV; previous treatment with IFN-based therapy or any investigational anti-HCV agent; systemic antiviral therapy within the previous 3 months; history or evidence of medical condition associated with chronic liver disease other than HCV; absolute neutrophil count < 1.5 x 10^9 cells/L; platelet count < 90 x 10^9 cells/L; haemoglobin concentration < 12 g/dL in women (< 13 g/dL in men); history of renal disease, serum creatinine > 1.5 times the ULN, an estimated creatinine clearance ≤ 70 mL/min or microproteinuria.
Interventions	Participants were randomised in a 1:1 ratio. 166 participants received at least 1 dose.

JUMP-C 2013 *(Continued)*

	Experimental group: oral mericitabine (Genentech, San Francisco, CA) 1000 mg twice a day for 24 weeks in participants with eRVR (defined as undetectable HCV RNA from week 4 through 22) or for 48 in participants without eRVR. **Control group:** placebo twice a day. **Co-intervention:** peg-IFN α-2a (40 kD) (Pegasys; Roche, Basel,Switzerland) 180 lg subcutaneously once-weekly and oral RBV (Copegus; Roche) at a dosage of 1000 (body weight: < 75 kg) or 1200 mg/day (body weight: > 75 kg) in 2 divided doses for 24 or 48 weeks.
Outcomes	Proportion of participants with undetectable plasma HCV RNA 24 weeks after the end of treatment (SVR24), with SAE, AEs, mortality.
Notes	We emailed Pockros and colleagues on 06 June 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list was maintained by the sponsor, and neither study personnel nor investigators had access to the list
Allocation concealment (selection bias)	Low risk	Participants were randomised by an interactive voice-response system. A computer-generated randomisation list was maintained by the sponsor, and neither study personnel nor investigators had access to the list
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinding was achieved through the use of matching placebo tablets. Investigators were advised byinteractive voice-response system at week 24 as to whether a participant was to stop treatment (mericitabine-treated participants with an eRVR) or continue to week 48 (mericitabine-treated participants without an eRVR and all placebo-treated participants). JF: "I guess that all participants were not blinded to maximum-follow up then? Since it would be obvious that the ones who stopped treatment after 24 weeks, received the study drug?"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial authors reported that only 55 participants in the experimental group completed 24 weeks of follow-up. It seems like there are 81 participants in the included analysis of SVR24. The trial authors do not account for how they imputed the participants with missing data
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported on
Vested-interest bias	Unclear risk	This research was funded by F. Hoffmann-La Roche Ltd.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Kwo 2010a1

Methods	An open-label, randomised, multicenter, parallel group, phase II trial (SPRINT-1) (NCT00423670)

Kwo 2010a1 *(Continued)*

Participants	520 participants **Country**: USA, Canada, and Europe **Inclusion criteria:** chronic hepatitis C infection genotype 1 treatment-naive, 18-60 years. Liver biopsy consistent with chronic HCV infection within 5 years of enrolment, haemoglobin ≥ 130 g/L (men), ≥ 120 g/L (women), neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L. Bilirubin, albumin, and creatinine within normal limits. **Exclusion criteria:** decompensated liver cirrhosis, HIV infection, previous organ transplantation, other causes of liver disease, pre-existing psychiatric disease, seizure disorder, cardiovascular disease, haemoglobinopathies, haemophilia, poorly controlled diabetes, autoimmune diseases **Group 1:** 104 participants Sex: 70 men (67%), 34 women (33%) Mean age ± SD: 48.3 ± 6.9 years Race: 83 white (80%), 2 American Indian or Alaskan (2%), 3 Asian (3%), 16 black (15%), 0 multiracial Weight, mean ± SD (kg): 83.4 ± 16.2 HCV genotype, n(%): 1a: 53(51), 1b: 42(40), 1, no subtype: 9(9) Baseline HCV RNA: $\log_{10}$ of geometric mean: 6.53. > 600,000 IU/mL, n(%): 94(90). Cirrhosis, n(%): 8(8) **Group 2:** 103 participants Sex: 51 men (50%), 52 women (50%) Mean age ± SD: 47.7 ± 7.4 Race: 85 white (83%), 1 American Indian or Alaskan (1%), 1 Asian (1%), 15 black (15%), 1 multiracial (1%) Weight, mean ± SD (kg): 79.9 ± 14.2 HCV genotype, n(%): 1a: 53(51), 1b: 37(36), 1, no subtype: 13(13) Baseline HCV RNA: $\log_{10}$ of geometric mean: 6.53. > 600,000 IU/mL, n(%): 90(87), cirrhosis, n(%): 7(7) **Group 3:** 103 participants Sex: 58 men (56%), 45 women (44%) Mean age ± SD: 47.6 ± 8.3 years Race: 85 white (83%), 1 American Indian or Alaskan (1%), 2 Asian (2%), 15 black (15%), 0 multiracial Weight, mean ± SD (kg): 78.4 ± 16.5 HCV genotype, n(%): 1a: 60(58). 1b: 35(34). 1, no subtype: 8(8) Baseline HCV RNA: $\log_{10}$ of geometric mean: 6.53. > 600,000 IU/mL, n(%): 93(90), cirrhosis, n(%): 6(6) **Group 4:** 107 participants Sex: 63 men (59%), 44 women (41%) Mean age ± SD: 46.4 ± 8.0 years Race: 86 white (80%), 0 American Indian or Alaskan, 2 Asian (2%), 18 black (17%), 1 multiracial (1%) Weight, mean ± SD (kg): 83.4 ± 17.3

Kwo 2010a1 *(Continued)*

	HCV genotype, n(%): 1a: 67(63), 1b: 30(28), 1, no subtype: 10(9) Baseline HCV RNA: log_{10} of geometric mean: 6.64. > 600,000 IU/mL, n(%): 98(92), cirrhosis, n(%): 7(7) **Group 5:** 103 participants Sex: 63 men (61%), 40 women (39%) Mean age ± SD: 46.7 ± 8.8 Race: 87 white (84%), 0 American Indian or Alaskan, 1 Asian (1%), 14 black (14%), 1 multiracial (1%) Weight, mean ± SD (kg): 80.0 ± 19.4 HCV genotype, n(%): 1a: 55(53), 1b: 36(35), 1, no subtype: 12(12) Baseline HCV RNA: log_{10} of geometric mean: 6.54. > 600,000 IU/mL, n(%): 94(91), cirrhosis, n(%): 9(9).
Interventions	**Experimental group:** 2: oral boceprevir 800 mg 3 times per day, starting at week 5 for a total of 24 weeks. 3: oral boceprevir 800 mg 3 times per day, starting at week 5 for a total of 44 weeks. 4: oral boceprevir 800 mg 3 times per day for a total of 28 weeks. 5: oral boceprevir 800 mg 3 times per day for a total of 48 weeks. **Control group:** 1: no intervention. **Co-interventions:** 1-5: peg-IFN α-2b 1.5 µg/kg body weight subcutaneously once weekly - weight-based oral RBV from 800-1400 mg daily (if body weight ≤ 65 kg dosage is 800 mg (400 mg twice daily); if body weight is 66-80 kg dosage is 1000 mg daily (400 mg in the morning and 600 mg in the evening); if body weight is 81-105 kg dosage is 1200 mg daily (600 mg twice daily); and if body weight is > 105 kg dosage is 1400 mg daily (600 mg in the morning and 800 mg in the evening)).
Outcomes	**Primary outcome:** SVR, defined as the proportion of participants with undetectable HCV RNA 24 weeks after discontinuation of treatment. **Secondary outcomes:** 1. number of participants with SVR based on a 4-week lead-in treatment with peg-IFN and RBV 2. number of participants with SVR based on duration of boceprevir treatment 3. number of participants negative for HCV RNA at week 12 4. number of participants negative for HCV RNA at 72 weeks post randomisation 5. number of participants with an EVR that achieved SVR 6. number of participants with a virologic response at week 12 that achieved SVR 7. number of participants with a virologic response at 72 weeks post randomisation that achieved SVR.
Notes	2 additional groups were present in the trial (Groups 6 and 7), which were randomised separately, but did not satisfy inclusion criteria, therefore were not included. We emailed Kwo and colleagues on 26 April 2016 for further explanation on difference between number of SAE stated in published article compared to results published on www.ClinicalTrials.gov but reply not received yet.

Risk of bias

Kwo 2010a1 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Low risk	Allocation performed by an external randomisation centre through interactive voice-response system in 1:1:1:1:1 ratio. Randomisation was stratified according to race (black vs non-black) and cirrhosis status (cirrhosis vs no cirrhosis).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial described as open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial described as open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Although number and reasons for withdrawal were clearly stated, the proportion of participants who discontinued treatment was high, from 26% to 50%, mostly due to AEs or treatment inefficiency.
Selective reporting (reporting bias)	High risk	Although a protocol was available and published before randomisation began, number of SAE were differently stated in the published article compared to data presented on www.ClinicalTrials.gov. Data presented in the latter were somewhat higher. Data reported are from www.ClinicalTrials.gov.
Vested-interest bias	High risk	The sponsor of the study contributed to patient recruitment, trial management, data collection, statistical analyses, and the writing and review of the report.
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias.

Kwo 2010a2

Methods	For characteristics see Kwo 2010a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code

Kwo 2010a2 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation performed by an external randomisation centre through interactive voice-response system in 1:1:1:1:1 ratio. Randomisation was stratified according to race (black vs non-black) and cirrhosis status (cirrhosis vs no cirrhosis)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial described as open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial described as open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Although number and reasons for withdrawal were clearly stated, the proportion of participants who discontinued treatment was high, from 26% to 50%, mostly due to AEs or treatment inefficiency.
Selective reporting (reporting bias)	High risk	Although a protocol was available and published before randomisation began, number of SAE were differently stated in the published article compared to data presented on www.ClinicalTrials.gov. Data presented in the latter were somewhat higher. Data reported are from www.ClinicalTrials.gov
Vested-interest bias	High risk	The sponsor of the study contributed to patient recruitment, trial management, data collection, statistical analyses, and the writing and review of the report
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Kwo 2010a3

Methods	For characteristics see Kwo 2010a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Low risk	Allocation performed by an external randomisation centre through interactive voice-response system in 1:1:1:1:1 ratio. Randomisation was stratified according to race (black vs non-black) and cirrhosis status (cirrhosis vs no cirrhosis)
Blinding of participants and personnel (performance bias)	High risk	Trial described as open-label

Kwo 2010a3 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial described as open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Although number and reasons for withdrawal were clearly stated, the proportion of participants who discontinued treatment was high, from 26% to 50%, mostly due to AEs or treatment inefficiency
Selective reporting (reporting bias)	High risk	Although a protocol was available and published before randomisation began, number of SAE were differently stated in the published article compared to data presented on www.ClinicalTrials.gov. Data presented in the latter were somewhat higher. Data reported are from www.ClinicalTrials.gov
Vested-interest bias	High risk	The sponsor of the study contributed to patient recruitment, trial management, data collection, statistical analyses, and the writing and review of the report
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Kwo 2010a4

Methods	For characteristics see Kwo 2010a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Low risk	Allocation performed by an external randomisation centre through interactive voice-response system in 1:1:1:1:1 ratio. Randomisation was stratified according to race (black vs. non-black) and cirrhosis status (cirrhosis vs. no cirrhosis)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial described as open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial described as open-label

Kwo 2010a4 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Although number and reasons for withdrawal were clearly stated, the proportion of participants who discontinued treatment was high, from 26% to 50%, mostly due to AEs or treatment inefficiency
Selective reporting (reporting bias)	High risk	Although a protocol was available and published before randomisation began, number of SAE were differently stated in the published article compared to data presented on www.ClinicalTrials.gov. Data presented in the latter were somewhat higher. Data reported are from www.ClinicalTrials.gov
Vested-interest bias	High risk	The sponsor of the study contributed to patient recruitment, trial management, data collection, statistical analyses, and the writing and review of the report
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Lalezari 2011

Methods	Randomised clinical trial
Participants	64 participants **Mean age:** 50 years **Country:** USA **Inclusion criteria:** treatment-naive adult participants with chronic hepatitis C.
Interventions	**Experimental group:** oral 200 mg, 400 mg, 800 mg of ACH-1625 for 28 days. **Control group:** placebo. **Co-intervention:** peg-IFN-α 2a/RBV.
Outcomes	Pharmacokinetics, HCV RNA, safety assessment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as placebo-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as placebo-blinded but it was unclear how the blinding was performed

Lalezari 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	Unclear risk	Not described
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Lalezari 2012

Methods	Randomised clinical trial
Participants	41 adult participants **Sex:** 29 men, 12 women **Mean age:** 48 years **Country:** USA **Inclusion criteria:** male or female adults 18-65 years of age, inclusive; a documented clinical history compatible with chronic hepatitis C, including the presence of HCV RNA in the plasma for least 6 months and a liver biopsy sample within 24 months with histology consistent with chronic HCV infection; HCV genotype 1, plasma HCV RNA > 5 log10 IU/ml, and anti-HCV antibody positive at screening; and agreement by participants to use a double-barrier method of birth. Sex: 29 men, 12 women. **Exclusion criteria:** BMI > 32 kg/m2; pregnancy or breastfeeding; co-infection with HBV or HIV; history or evidence of decompensated liver disease; history of HCC or findings suggestive of possible HCC; other causes of liver disease; previous antiviral treatment for HCV infection; current abuse of alcohol or illicit drugs or treatment for opioid addiction; use of any known inhibitor and/or inducer of CYP 3A4 or any other investigational drugs within 30 days of dosing; abnormal laboratory values at screening (a hemoglobin level < 12.0 g/dl for males or < 11.0 g/dl for females; an absolute neutrophil count < 1.5 × 10^9/liter; a platelet count < 130 × 10^9/liter; an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level > 2.5 × upper limit of normal [ULN]; an alkaline phosphatase level > 1.25 × ULN; an albumin level < 3.5 g/dl; total bilirubin, amylase, lipase, or international normalized ratio [INR] > ULN; a serum creatinine or blood urea nitrogen value > ULN; creatinine clearance < 80 ml/min as estimated by the Cockcroft-Gault formula; or any other laboratory abnormality > grade 1, except for asymptomatic cholesterol or triglycerides); or other clinically significant diseases that, in the opinion of the investigator, would jeopardize the safety of the patient or impact the validity of the study results.
Interventions	**Experimental group:** oral 25 mg, 50 mg, 75 mg, 100 mg of IDX184 for 3 days. **Control group:** placebo. **Co-intervention:** 14 days after treatment the participants were offered extended therapy with peg-IFN/RBV.
Outcomes	Safety assessment, antiviral activity.
Notes	We emailed Lalezari and colleagues on 26 April 2016 for additional information but reply not received yet.

Lalezari 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only some outcomes were blinded for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Idenix pharmaceuticals Inc
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Lalezari 2013

Methods	Randomised clinical trial
Participants	81 adult participants **Sex:** 56 men, 25 women **Mean age:** 48 years **Country:** USA **Inclusion criteria:** male or female participants 18-65 years old; documented clinical history compatible with chronic hepatitis C, including positive anti-HCV antibody or presence of HCV RNA in the plasma for at least 6 months and liver biopsy within 24 months with histology consistent with chronic hepatitis C infection; HCV-genotype 1, plasma HCV RNA> 5 $\log_{10}$ IU/mL; all participants agreed to use double-barrier birth control (such as condom plus spermicide) from screening through at least 6 months after the last dose of the study drug. **Exclusion criteria:** pregnancy or breastfeeding; BMI > 35 kg/m2; co-infection with HBV or HIV; history or evidence of decompensated liver disease; prior clinical or histological evidence of cirrhosis; ALT or AST level > 3 ULN; histology of HCC or findings suggestive of possible HCC; 1 or more additional known primary or secondary causes of liver disease, other than hepatitis C, previous antiviral treatment for HCV; current abuse of alcohol or illicit drugs; current use of any major inhibitor or inducer of cytochrome P450 3A4 or any other investigational drugs within 30 days of dosing, or other clinically sig-

Lalezari 2013 *(Continued)*

	nificant diseases that, in the opinion of the investigator, would jeopardise the safety of the participants or affect the validity of the study results.
Interventions	**Experimental groups:** oral rising daily doses of 50, 100, 150 or 200 mg of IDX184 for 2 weeks. **Control group:** placebo. **Co-intervention:** peg-IFN- α 2a and RBV for 2 weeks. All participants received additional 2 weeks of peg-IFN and RBV.
Outcomes	HCV RNA, Safety, pharmacokinetics.
Notes	We emailed Lalezari and colleagues on 26 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Despite being a double-blinded study, there were different doses, syringes plus capsules, different administrations – once vs twice
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of dropouts was unclear
Selective reporting (reporting bias)	High risk	Not all outcomes stated in the protocol were assessed (NCT01011166)
Vested-interest bias	High risk	The trial was funded by Idenix Pharmaceuticals Inc.
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Larrey 2012

Methods	Randomised phase I clinical trial
Participants	27 participants **Sex:** 21 men, 6 women **Mean age:** 46 years **Countries:** France, Germany, and Switzerland.

Larrey 2012 *(Continued)*

	Inclusion criteria: treatment-naive participants male or female (with documented hysterectomy or postmenopausal), 18–70 years of age, had chronic hepatitis C infection of genotype-1, with a HCV viral load > 100,000 IU/mL at screening. **Exclusion criteria:** cirrhosis was ruled out by biopsy or elastometry (FibroScan; cut-off used by investigators ranged from 12.5 to 16.0 kPa) performed within 24 months prior to study enrolment. Participants with HBV or HIV co-infection, concurrent liver disease other than HCV, past treatment with any experimental polymerase inhibitor, or hyperbilirubinaemia (> 1.5 ULN not due to Gilbert's polymorphism).
Interventions	**Experimental group:** oral 400 mg, 600 mg, or 800 mg 3 times daily of BI 207127 for 28 days. **Control group:** placebo. **Co-intervention:** peg-IFN α-2a was administered subcutaneously at a dose of 180 lg per week, and RBV was given orally at a dose of 1000 mg per day (body weight < 75 kg) or 1200 mg per day (body weight > 75 kg) in 2 divided doses. Participants were advised to use sun protection. After 4 weeks, participants were given the opportunity to continue peg-IFN α-2a or 2b and RBV up to week 48 at the investigators' discretion.
Outcomes	Efficacy assessment, safety assessment, drug resistance monitoring, HCV RNA, PK assessment.
Notes	NCT00905632 Only treatment-naive participants received placebo, and could be used in the analyses. We emailed Larrey and colleagues on 26 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants in the treatment-naive group were lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol (NCT00905632) were assessed
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Larrey 2013

Methods	Randomised clinical trial
Participants	60 participants **Sex:** 48 men, 12 women **Mean age:** 50.2 years **Inclusion criteria:** treatment-naive or treatment-experienced participants without cirrhosis or treatment-experienced participants with compensated cirrhosis female, aged 18-70 years, with confirmed chronic HCV genotype 1 infection. Deleobuvir had shown activity against HCV genotype 1a and 1b in vitro; therefore, participants with either subgenotype were eligible. All participants had an HCV RNA level > 100,000 IU/mL at screening. The treatment-experienced group included previous null responders, partial responders, and relapsers. The presence or absence of cirrhosis was confirmed by liver biopsy or transient elastography (Fibroscan 12.5 kPa). **Exclusion criteria:** hepatitis B or HIV co-infection, concurrent liver disease other than HCV, past treatment with any experimental polymerase inhibitor, planned or concurrent use of any other approved or investigational pharmacological therapy, or current drug or alcohol abuse. Participants were also excluded if they had hyperbilirubinaemia, abnormal hematologic or laboratory values at screening, or concurrent disease considered clinically significant by the investigator.
Interventions	**Experimental group:** rising doses of 100 mg, 200 mg, 400 mg, 800 mg, and 1200 mg every 8 h of deleobuvir (BI 207127). **Control group:** placebo.
Outcomes	N25B variants, safety assessment, pharmacokinetics.
Notes	We emailed Larrey and colleagues on 26 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded but method was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded but method was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described (it was described that 3 participants dropped out due to AEs)
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed

Larrey 2013 *(Continued)*

Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2008

Methods	Randomised clinical trial
Participants	33 participants **Sex:** 28 men, 5 women **Mean age:** not described. **Inclusion criteria:** treatment-naive and treatment-experienced noncirrhotic participants,18-55 years old, with high viral load, genotype 1, chronic HCV infection.
Interventions	**Experimental group:** oral 125 mg, 600 mg of MK-7009 once daily for 8 days or 25 mg, 75 mg, 250 mg, or 500 mg of MK-7009 twice daily for 8 days. **Control group:** placebo.
Outcomes	HCV RNA, safety assessment.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on random, blinding, missing data, protocol, data, participants' characteristics, funding, number of participants in placebo/exp group but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as placebo-blinded, but it was not described how blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as placebo-blinded, but it was not described how blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Several authors worked for several pharmaceutical companies

Lawitz 2008 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2009

Methods	Randomised clinical trial
Participants	40 participants **Sex:** not reported **Mean age:** not reported **Country:** USA **Inclusion criteria:** participants both treatment-naive and treatment-experienced with chronic HCV 1
Interventions	The trial was divided into 4 cohorts, with different experimental intervention. **Experimental group:** oral 100 mg or 200 mg of VCH-916 3 times daily for 14 days. Oral 300 or 400 mg of VCH-916 twice daily for 3 days. **Control group:** placebo.
Outcomes	Safesty assessment, HCV RNA level, pharmacokinetics
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on random, blinding, missing data, protocol, data, participants characteristics, funding, number of participants in placebo/exp group but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded, but it was not described how blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but it was not described how blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	Unclear risk	Not described

Lawitz 2009 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2010a

Methods	Randomised clinical trial
Participants	54 participants **Country:** USA **Inclusion criteria:** Adult treatment-naive participants in genotype 1 HCV participants.
Interventions	**Experimental group:** oral 25 mg, 75 mg, or 200 mg of GS-9256 twice daily, or 300 mg of GS-9256 once daily for 3 days. **Control group:** placebo.
Outcomes	Safesty assessment, HCV RNA level, pharmacokinetics.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on random, blinding, missing data, protocol, data, participants characteristics, funding, number of participants in placebo/exp group but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded, but it was not described how blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but it was not described how blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Several authors worked for Gilead Sciences
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2010b

Methods	Randomised clinical trial
Participants	63 participants **Inclusion criteria:** non-cirrhotic treatment-naive adult participants with genotype 1 HCV participants. **Exclusion criteria:** not described.
Interventions	The trial used 3 cohorts **Experimental group:** oral 100 mg, 200 mg, or 400 mg of PSI-7977 once daily for 28 days. **Control group:** placebo. **Co-intervention:** epg-IFN/RBV.
Outcomes	HCV RNA level, pharmacokinetics.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on random, blinding, missing data, protocol, data, participants characteristics, funding, number of participants in placebo/exp group but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded, but it was not described how blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but it was not described how blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Main author worked for several pharmaceutical companies
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2010c

Methods	Randomised clinical trial
Participants	63 participants **Inclusion criteria:** participants received at least 1 dose of the drug and in cohort 200 mg twice a day adults with hepatitis C genotype 1.
Interventions	**Experimental group:** 200 mg or 400 mg of ANA598 twice a day. **Control group:** placebo. **Co-intervention:** 12 weeks of standard of care treatment.
Outcomes	Safety, antiviral activity, pharmacokinetics.
Notes	Only the cohort with 200 mg is reported here. We emailed Lawitz and colleagues on 26 April 2016 for additional information on sequence generation, blinding, incomplete outcome data, number of deaths, SVR24 but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind and placebo controlled, but the placebo was not further described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants were actually randomised to the experimental and control group and therefore, it is unclear how many participants are with missing data
Selective reporting (reporting bias)	High risk	The trial did not report on the level of RBV and peg-IFN in the blood as is stated in the protocol (NCT00978497)
Vested-interest bias	High risk	The trial was supported by a company with an interest in a given result Hoffmann-La Roche
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of other bias

Lawitz 2011a

Methods	Randomised clinical trial
Participants	35 participants

Lawitz 2011a *(Continued)*

	Sex: 25 men, 10 women **Mean age:** 50 years **Country:** USA **Inclusion criteria:** treatment-naive adults diagnosed with hepatitis C genotype 1. **Exclusion criteria:** not described.
Interventions	The trial used different experimental groups, with different doses of ABT-450. **Experimental group:** 50 mg ABT-450 + 100 mg RBV, 100 mg ABT-450 + 100 mg RBV, 200 mg ABT-450 + 100 mg RBV once daily for 3 days. **Control group:** placebo. **Co-intervention:** peg-IFN α-2a 180 mg/week + weight-based RBV 1000–1200 mg/day (standard of care) for 12 weeks. After week 12, participants received standard of care treatment alone for 36 weeks.
Outcomes	Safety assessment, HCV RNA level, pharmacokinetics.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on randomisation, blinding, missing data, protocol, data, funding, IL28b data but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as placebo-controlled, but it was not described how blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as placebo-controlled, but it was not described how blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out of the placebo group
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Several authors worked for Gilead Sciences
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2011b

Methods	Randomised clinical trial
Participants	252 participants **Sex:** 151 men, 101 women **Countries:** USA and Europe. **Inclusion criteria:** non cirrhotic treatment-naive adult participants with chronic hepatitis C genotype 1. **Exclusion criteria:** not described.
Interventions	**Experimental group 1:** oral tegobuvir 40 mg twice daily for 48 weeks. **Experimental group 2:** oral tegobuvir 40 mg response-guided for 24-48 weeks. **Control group:** placebo. **Co-intervention**: peg/RBV.
Outcomes	Safety assessment, pharmacokinetics, HCV RNA.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on randomisation, blinding, missing data, protocol, complete trial, data, funding but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as placebo-controlled, but it was not described how blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as placebo-controlled, but it was not described how blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% percent dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Several authors worked for Gilead Sciences
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2012a

Methods	Randomised clinical trial
Participants	72 adult participants **Sex:** 52 men, 20 women **Mean age:** 48 years **Country:** USA **Inclusion criteria:** 18–65 years of age, with chronic infection with genotype 1a or 1b HCV virus and plasma HCV RNA > 5 $\log_{10}$ IU/mL at screening. Participants were HCV treatment-naive and had a BMI of 19–35 kg/m2 inclusive, creatinine clearance > 70 mL/min, and a QTcF interval < 450 ms. **Exclusion criteria:** known cirrhosis, hepatic decompensation, excessive ongoing alcohol intake, Gilbert's syndrome, evidence of HCC, co-infection with HIV or HBV, prothrombin time > 1.5 ULN, albumin < 3 g/dL, ALT and AST levels > 5 ULN, total bilirubin > ULN, hemoglobin < 11 g/dL, platelets < 90,000/mm3, or absolute neutrophil count < 1000 cells/mm3 (< 900 cells/mm3 for African Americans). Concomitant prescription or non-prescription medications were prohibited during the study unless prior approval was received from the medical monitor. The only exception was the use of hormonal contraception; additional double barrier method contraception was mandated for all women of childbearing potential.
Interventions	The trial was divided into 6 different cohorts, and randomised to experimental intervention or placebo. **Experimental group:** oral 1 mg, 3 mg, 10 mg (genotype 1a), 10 mg (genotype 1b), 30 mg, or 90 mg of GS-5885 for 3 days. **Control group:** placebo.
Outcomes	Safety assessment, pharmacokinetics, HCV RNA, viral sequencing.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on allocation, blinding, protocol, separate data from IL28b but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation schedule generated via computer by the sponsor's Biometrics group
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded, but it was not described how blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, but it was not described how blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 person dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	This trial was supported by Gilead Sciences

Lawitz 2012a *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2012b

Methods	Randomised clinical trial
Participants	90 participants **Country:** USA **Inclusion criteria:** treatment-naive adult participants with chronic hepatitis C genotype 1. **Exclusion criteria:** not described.
Interventions	The trial was divided into 9 cohorts **Experimental group:** oral 50 mg, 100 mg, or 300 mg of GS-6620 once daily administered for 5 days. Oral 100 mg, 300 mg, or 900 mg of GS-6620 once daily administered for 5 days. Oral 450 mg or 900 mg of GS-6620 twice daily administered for 5 days. **Control group:** placebo.
Outcomes	Safety assessment, pharmacokinetics, HCV RNA
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on randomisation, blinding, missing data, protocol, data, funding, SAE (non-treatment related) but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as placebo-controlled, but it was not described how blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as placebo-controlled, but it was not described how blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Several authors worked for Gilead Sciences

Lawitz 2012b *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2013a1

Methods	Randomised clinical trial
Participants	122 participants **Sex:** 73 men, 49 women **Mean age:** 49.4 years **Country:** USA **Inclusion criteria:** treatment-naive participants HCV genotypes 1 had to have an HCV RNA concentration of 50,000 IU/mL or greater. HCV genotypes participants had a liver biopsy within 36 months before enrolment. Inclusion criteria also included the following haematological and biochemical laboratory variables: a neutrophil count of 1.5×10^9/L (or $\geq 1.25 \times 10^9$/L for black participants), a haemoglobin concentration of 11 g/dL or higher in women or 12 g/dL or higher in men, a platelet count of greater than 90×10^9/L, total bilirubin within 2 times the ULN (21 µmol/L), and an albumin concentration of 30 g/L or lower. **Exclusion criteria:** cirrhosis, HBV or HIV, psychiatric illness, pulmonary or cardiac disease, seizure disorder, or other serious comorbid disorders.
Interventions	**Experimental group:** oral 200 mg, or 400 mg of sofosbuvir once daily for 12 weeks. **Control group:** placebo. **Co-intervention:** 48 weeks of peg-IFN 180 µg per week subcutaneously; RBV was dosed according to weight (ie, participants < 75 kg received 1000 mg and those > 75 kg received 1200 mg; RBV was given in 2 daily doses. 400 mg in the morning and 600 mg in the evening for participants receiving 1000 mg a day, or 600 mg in the morning and 600 mg in the evening for participants receiving 1200 mg a day).
Outcomes	Virological response, pharmacokinetics, AEs.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Low risk	Interactive online response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias)	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed

Lawitz 2013a1 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	High risk	The trial added additional secondary outcomes
Vested-interest bias	High risk	The trial was funded by Gilead Sciences
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2013a2

Methods	For characteristics see Lawitz 2013a1	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Low risk	Interactive online response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	High risk	The trial added additional secondary outcomes
Vested-interest bias	High risk	The trial was funded by Gilead Sciences

Lawitz 2013a2 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2013b

Methods	Randomised clinical phase I, multicentre trial
Participants	44 participants **Sex:** 32 men, 9 women **Median age:** 49 years **Country:** USA **Inclusion criteria:** 18-65 years of age and had chronic HCV 1a or 1b and plasma HCV RNA > 5 $\log_{10}$ IU/mL at screening. Participants were HCV treatment-naive and had a BMI of 19-35 kg/m^2 inclusive, creatinine clearance > 60 mL/min and a QTcF interval < 450 ms. **Exclusion criteria:** cirrhosis, hepatic decompensation, excessive ongoing alcohol intake, Gilbert's syndrome, evidence of HCC, co-infection with HIV or HBV, ALT or AST levels > 5 x ULN, total bilirubin > ULN, haemoglobin < 11 g/dL, or absolute neutrophil count 1000 cells/mm^2 (750 cells/mm^2). Concomitant prescription during the study unless prior approval was received from the medical monitor. Participants using hormonal contraception were required to employ 2 additional barrier methods of contraception.
Interventions	The trial divided into 4 cohorts, and randomised to experimental group or control group **Experimental group:** oral 60 mg, 200 mg (genotype 1a), 200 mg (genotype 1b), or 400 mg of GS-9451 once daily for 3 days. **Control group:** placebo.
Outcomes	Antiviral response, sequence analyses, pharmacokinetics, safety assessment.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on allocation, blinding (placebo pill), protocol but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was described that all were blinded, however it was not stated if there were any similarities between the placebo pill and intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was described that all were blinded, however it was not stated if there were any similarities between the placebo pill and intervention

Lawitz 2013b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were above 5% dropouts. 3 participants were not included in the efficacy analyses. In addition, 3 participants were withdrawn after enrolment and not included in any analysis due to unknown reasons. It was unclear how the trial handled missing data.
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Gilead Sciences
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2013c

Methods	Randomised phase IIb clinical trial
Participants	211 participants **Sex:** 131 men, 80 women **Mean age:** 49.5 years **Countries:** Australia, Austria, Belgium, Canada, Chile, Czech Republic, France, Germany, Israel, Korea, Lithuania, New Zealand, Poland, South Korea, Sweden, Taiwan, Thailand, UK, and USA **Inclusion criteria:** treatment-experienced non-cirrhotic adults chronic genotype 1 HCV-infected participants whose previous treatments with P/R had failed, a minimum of 25% of participants prior null responders, men and women 18–65 years of age, and baseline HCV RNA > 4 x 10^5 IU/mL. **Exclusion criteria:** non-HCV-related chronic hepatitis, HIV co-infection, evidence of cirrhosis on liver biopsy or approved non-invasive imaging, or any other condition contraindicated for treatment with P/R
Interventions	4 different experimental arms **Experimental group 1**: oral MK-7009 600 mg twice daily for 24 weeks. **Experimental group 2:** oral MK-7009 600 mg twice daily for 24 weeks and 24 weeks of placebo for 24 weeks. **Experimental group 3:** oral MK-7009 300 mg twice daily for 48 weeks. **Experimental group 4:** oral MK-7009 600 mg twice daily for 48 weeks. **Control group:** placebo for 48 weeks. **Co-intervention:** peg-IFN 180 µg weekly and RBV 1000–1200 mg/day for 24–48 weeks.
Outcomes	Safety assessment, SVR.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on randomisation, blinding, dealing with missing data, baseline characteristics for IL28B genotype but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement

Lawitz 2013c *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Above 5% dropouts, and it was unclear how the trial handled missing data
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported on. NCT00704405
Vested-interest bias	High risk	The trial was funded by Merck, Sharp & Dohme Corp
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2013d

Methods	Randomised clinical trial
Participants	40 participants **Sex:** 36 men, 4 women **Mean age:** 43 years **Country:** USA **Inclusion criteria:** treatment-naive ages between 18 and 65 years, non-cirrhotic chronic HCV genotype 1 infection and HCV RNA levels of 50,000 IU/mL ages with BMIs ranging from 18-36 kg/m2 **Exclusion criteria:** women were to be surgically sterile, postmenopausal for at least 12 months at screening, or taking protocol-specified contraceptive measures. Positive for anti-hepatitis A virus immunoglobulin M (IgM) antibodies, hepatitis B surface antigen, anti-hepatitis B core protein IgM antibodies, or anti-HIV antibodies. No medication associated with QT interval prolongation was permitted within 30 days prior to dosing or during the study, and any other concurrent medication required approval by the investigator and the sponsor. Participants who had received any systemic antineoplastic or immunomodulatory treatment within 6 months prior to the first dose of study drug or who might have needed such treatments at any time.
Interventions	Participants were randomised in 4 cohorts with different doses of GS-9851 **Experimental group:** 3 days of either 50 mg, 100 mg, 200 mg, or 400 mg as oral intake of GS-9851. **Control group:** placebo.

Lawitz 2013d *(Continued)*

Outcomes	Pharmacokinetics, clinical virology assessment, safety and tolerability assessment.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on protocol, randomisation, blinding but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded, however it was not stated how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded, however it was not stated how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All completed the study
Selective reporting (reporting bias)	Unclear risk	It was stated that there was a protocol, however the protocol could not be found.
Vested-interest bias	High risk	The trial was funded by Pharmasset, Inc. Severina Moreira and Justin Cook of Niche Science and Technology Ltd.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2013e

Methods	Randomised clinical trial
Participants	40 participants **Sex:** 33 men, 7 women **Mean age:** 46 years **Country:** USA **Inclusion criteria:** participants aged 18–55 years with a BMI 18.5 to 636 kg/m2 and chronic, compensated, genotype1 HCV infection. All participants had a baseline HCV RNA > 106 IU/mL and no evidence of cirrhosis or bridging fibrosis (according to biopsy within 3 years of screening). Participants also had laboratory values within pre-specified criteria at study entry. **Exclusion criteria:** participants previously treated with approved HCV therapy or with a DAA for HCV, or with chronic HBV or HIV infection were excluded.

Lawitz 2013e *(Continued)*

Interventions	**Experimental group:** received different doses of vaniprevir orally, for 8 days twice daily (25 mg, 75 mg, 250 mg, 500 mg, 700 mg) or 8 days once daily (125 mg, 600 mg). **Control group:** matching placebo.
Outcomes	Safety, tolerability and efficacy, pharmacokinetics, medication adherence.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on allocation concealment, blinding of outcome assessors, sample size and protocol for trial 1 and 2 but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated centralised randomisation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo delivered in equal amounts
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only on person dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	This study was funded by Merck Sharp & Dohme Corp
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2013f

Methods	Randomised clinical trial
Participants	38 adult participants **Country:** USA **Inclusion criteria:** chronic hepatitis C genotype 1 either with cirrhosis, or without cirrhosis
Interventions	**Experimental group:** oral 100 mg or 400 mg of ACH-2684 once daily for 3 days. Oral 400 mg of ACH-2684 twice daily. **Control group:** placebo.

Lawitz 2013f *(Continued)*

Outcomes	Safety assessment, pharmacokinetics, HCV RNA.
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on randomisation, blinding, missing data, protocol, data, funding, SAE, participants in each group but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as placebo-controlled, but it was not described how blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as placebo-controlled, but it was not described how blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Several authors worked for Achillion pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2014a

Methods	Randomised clinical trial
Participants	100 participants **Sex:** 65 men, 35 women **Country:** USA **Inclusion criteria:** compensated cirrhotic adults with chronic HCV genotype 1 infection. **Exclusion criteria:** not described.
Interventions	**Experimenatal group:** oral 250 mg of GS-9669 once daily for 8 weeks or oral 500 mg of GS-9669 once daily for 8 weeks. **Control group:** RBV. **Co-intervention:** ledipasvir and sofosbuvir.

Lawitz 2014a *(Continued)*

Outcomes	Adverse events, HCV RNA SVR12
Notes	We emailed Lawitz and colleagues on 26 April 2016 for additional information on random, blinding, missing data, protocol, data separate from the groups, participants characteristics, funding, IL28b-databut reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	Several authors worked for several pharmaceutical companies
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Lawitz 2015

Methods	Randomised clinical trial
Participants	85 adult participants **Sex:** 68 men, 19 women **Mean age:** 47 years **Countries:** USA and Puerto Rico **Inclusion criteria:** 18–65 years, with treatment-naive chronic genotype 1–6 HCV infection and HCV RNA levels ≥5 log10 IU/mL at screening. Participants were required to have a BMI of 19–34 kg/m2 inclusive, creatinine clearance > 70 mL/min and QTcF ≤450 ms for men and ≤470 ms for women. **Exclusion criteria:** co-infected with HBV or HIV, had prior treatment with a HCV NS5Ainhibitor, evidence of cirrhosis or HCC, history of clinical hepatic decompensation (e.g. ascites, jaundice, encephalopathy or variceal haemorrhage) or any other clinically significant condition other than chronic HCV infection.

Lawitz 2015 *(Continued)*

Interventions	The trial was divided into 11 dosing cohorts: 5 cohorts of participants with genotype 1a infection; 1 cohort of participants with genotype 1b infection, 1 cohort of participants with genotype 2 infection, 3 cohorts of participants with genotype 3 HCV infection and 1 cohort of participants with genotype 4 HCV infection. **Experimental group:** oral GS-5816 (5 mg, 25 mg, 50 mg, 100 mg, 150 mg). **Control group:** matching placebo.
Outcomes	Safety assessment, efficacy analysis, pharmacokinetic analysis.
Notes	ClinicalTrials.gov number: NCT01740791. The trial reported that 87 participants were randomised, however it was also stated that those with genotype 4 (n = 2) were not randomised. Therefore we could not use data from the combined 150 mg group, as the non-randomised genotype 4 participants were included in this group. We emailed Lawitz and colleagues on 26 April 2016 for additional information on allocation, blinding, how the trial handled missing data but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation scheme, by the sponsor
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were more than 5% dropouts and it was unclear how the trial handled missing data.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported on
Vested-interest bias	High risk	The study was funded by Gilead Sciences
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Liu 2015a

Methods	Randomised clinical phase Ib trial
Participants	48 participants **Sex:** 48 men **Country:** USA

Liu 2015a *(Continued)*

	Inclusion criteria: non-cirrhotic participants aged 18-60 years (up to 65 years old at the discretion of the investigator) with HCV RNA levels of > 100,000 IU/mL
Interventions	The trial was divided into cohorts, in which randomisation was performed **Experimental group:** 5 mg, 10 mg, and 50 mg once daily of MK-8742 for participants infected with genotype 1a or 1b, and 10 mg, 50 mg, and 100 mg once daily of MK-8742 for participants infected with genotype 3. **Control group:** placebo.
Outcomes	Activity, pharmacokinetics, safety
Notes	We emailed Liu and colleagues on 26 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	The trial did not assess safety (NCT01532973)
Vested-interest bias	High risk	The trial was funded by Merck Sharp & Dohme Corp
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Mallalieu 2014

Methods	Randomised clinical trial
Participants	35 participants **Sex:** 24 men, 11 women **Mean age:** 47.6 years

Mallalieu 2014 *(Continued)*

	Inclusion criteria: treatment-naive male or female participants with chronic hepatitis C aged 18-55 years, with a BMI of 18-35 were eligible for a multicenter, double-blind, randomised, placebo-controlled study. Participants were required to have HCV genotype 1a or 1b infection, a serum HCV RNA concentration greater than 75,000 IU/mL, a serum ALT concentration under 5 times the ULN, and compensated liver disease. **Exclusion criteria:** participants with evidence of cirrhosis or decompensated liver disease were excluded, as were participants with a history of or current alcohol abuse, poorly controlled insulin-dependent diabetes, unstable or poorly controlled asthma, congestive heart failure, unstable cardiopulmonary disease, renal disease, or seizure disorder. Eligible participants in all studies were required to have a negative urine drug screen, serum pregnancy test (if female), and to have a negative hepatitis B surface antigen test and anti-HIV antibody test. Pregnant and breast feeding female participants were ineligible. Other exclusion criteria included donation of 4500 mL of blood within 30 days (participants with chronic hepatitis C).
Interventions	**Experimental group:** sequential cohorts of participants were randomly assigned to receive setrobuvir 200 mg, 400 mg, or 800 mg twice a day for 3 days. **Control group:** received placebo for 3 days.
Outcomes	Safety, kinetics, antiviral activity.
Notes	5 participants originally enrolled in cohort 2 (400 mg twice a day) were dosed incorrectly. These participants received setrobuvir 200 mg twice a day and were thus included with cohort 1 in the analysis. We emailed Mallalieu and colleagues on 26 April 2016 for additional information random sequence generation + allocation, participants completing the study, blinding but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded but there was no further description of the placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear if any participants dropped out
Selective reporting (reporting bias)	Low risk	The trial reports all outcomes stated in the protocol (NCT00782353)
Vested-interest bias	High risk	The trial was sponsored by a company that might have an interest in a given outcome (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Manns 2011

Methods	Randomised clinical trial
Participants	53 participants were randomised **Sex:** 27 men, 7 women **Mean age:** 48.9 years **Inclusion criteria:** participants with chronic HCV infection of genotype-1 were recruited to the study, if they were treatment-naive (no prior therapy with IFN, peg-IFN, or RBV) or treatment-experienced (virologic failure during or after treatment with an approved dose of peg-IFN combined with RBV), had HCV RNA P100,000 IU/mL and were aged 18 years or older. **Exclusion criteria:** participants with liver cirrhosis, hyperbilirubinaemia (> 1.5x ULN; participants with Gilbert's disease were accepted), HIV, or HBV co-infection were excluded. Furthermore, participants who had previously received any treatment with a protease inhibitor and women of child-bearing potential not agreeing or able to use medically accepted contraception throughout the study were excluded.
Interventions	**Experimental group:** treatment-naive participants: BI201335 monotherapy (20 mg, 48 mg, 120 mg, and 240 mg once a day) for 14 days, participants with a HCV RNA decrease P1 log10 from baseline (on Day 10), BI201335 treatment was combined with peg-IFN α-2a (180 lg/week) and RBV (1000 mg or 1200 mg/day) from Days 14 to 28. **Control group:** placebo combined with peg-IFN α-2a and RBV. All participants were offered to extend standard of care to Week 48, with an additional 24 weeks of follow-up. **Co-intervention:** peg-IFN α-2a (180 lg/week) and RBV (1000 mg or 1200 mg/day).
Outcomes	**Primary:** virologic response, AEs, SAE, laboratory test abnormalities. **Secondary:** viral load reduction, change from baseline in viral load, rapid virological response, early virological response, complete early virological response 1+2, end of treatment response and SVR
Notes	We emailed Manns and colleagues on 26 April 2016 for additional information on allocation concealment, random sequence generation, unpublished data, dealing with missing data, SVR data and AE, il28b and blinding in general. Data on SAEs and non-SAEs distinguishing between treatment-naive and treatment-experienced but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded and but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.

Manns 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant dropped out (The reason for the discontinuation of 1 participant was the diagnosis of an unexpected pregnancy of his partner representing an exclusion criterion for treatment with RBV)
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT00793793) and all outcomes were reported on
Vested-interest bias	High risk	"Michael Manns has received grant support, contributed to clinical trials, and is a member of a speaker bureau and/or consulted for Schering Plough, Roche, Merck, Bristol-Myers Squibb, Vertex, Tibotec, Astra/Arrows, Novartis, Human Genome Sciences, Boehringer Ingelheim, and Valeant. Peter W. White, Jerry Stern, Gerhard Steinmann, Chan-Loi Yong, George Kukolj, Joe Scherer and Wulf O. Boecher are employees of Boehringer Ingelheim."
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Manns 2012a1

Methods	Randomised clinical trial
Participants	95 participants were randomised **Sex:** 55 men, 39 women **Mean age:** 46.2 years **Inclusion criteria:** adult, treatment-naive participants with chronic, compensated, HCV genotype 1 infection, defined as HCV RNA levels ≥ 4×10^5 IU/mL at screening (i.e. within 75 days preceding the first dose of vaniprevir or placebo), were enrolled. All participants had positive serology for HCV or detectable HCV RNA ≥ 6 months before study initiation. **Exclusion criteria:** Participants with evidence of cirrhosis by histology, imaging, or physical findings were excluded.
Interventions	**Experimental group:** 1. 300 mg twice a day plus open-label peg-IFN α-2a and RBV 180 µg/week + 1000 mg-1200 mg/day for 28 days. 2. 600 mg twice a day plus open-label peg-IFN α-2a and RBV 180 µg/week + 1000 mg-1200 mg/day for 28 days. 3. 600 mg once a day plus open-label peg-IFN α-2a and RBV 180 µg/week + 1000 mg-1200 mg/day for 28 days. 4. 800 mg once a day plus open-label peg-IFN α-2a and RBV 180 µg/week + 1000-1200 mg/day for 28 days. **Control group:** placebo plus open-label peg-IFN α-2a and RBV 180 µg/week + 1000 mg-1200 mg/day for 28 days. **Co-intervention:** peg-IFN α-2a and RBV 180 µg/week + 1000 mg-1200 mg/day.
Outcomes	**Primary:** proportion of participants achieving RVR. AEs and participants that discontinued due to AEs. Exploratory: proportion of participants achieving EVR, proportion of participants achieving SVR.
Notes	We emailed Manns and colleagues on 26 April 2016 for additional information on allocation concealment, unpublished data, correlation of il28b genotype data and SVR but reply not received yet.

Manns 2012a1 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation procedure by an interactive voice-response system
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as double-blinded to investigator and participant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15 participants dropped out
Selective reporting (reporting bias)	Unclear risk	A protocol was found (NCT00704184), primary objectives were reported correctly, secondary outcomes changed and new exploratory outcomes were reported in the paper
Vested-interest bias	High risk	This study was funded by Merck Scharp and Dohme Corp.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Manns 2012a2

Methods	For characteristics see Manns 2012a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation procedure by an interactive voice-response system
Allocation concealment (selection bias)	Unclear risk	Not described

Manns 2012a2 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as double-blinded to investigator and participant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15 participants dropped out
Selective reporting (reporting bias)	Unclear risk	A protocol was found (NCT00704184), primary objectives were reported correctly, secondary outcomes changed and new exploratory outcomes were reported in the paper
Vested-interest bias	High risk	This study was funded by Merck Scharp and Dohme Corp.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Manns 2012a3

Methods	For characteristics see Manns 2012a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation procedure by an interactive voice-response system
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as double-blinded to investigator and participant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias)	Unclear risk	15 participants dropped out

Manns 2012a3 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	A protocol was found (NCT00704184), primary objectives were reported correctly, secondary outcomes changed and new exploratory outcomes were reported in the paper.
Vested-interest bias	High risk	This study was funded by Merck Scharp and Dohme Corp.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Manns 2012a4

Methods	For characteristics see Manns 2012a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation procedure by an interactive voice-response system
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as double-blinded to investigator and participant
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15 participants dropped out
Selective reporting (reporting bias)	Unclear risk	A protocol was found (NCT00704184), primary objectives were reported correctly, secondary outcomes changed and new exploratory outcomes were reported in the paper.
Vested-interest bias	High risk	This study was funded by Merck Scharp and Dohme Corp.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Manns 2014a

Methods	A phase III, randomised, double-blind, placebo-controlled, parallel-design trial (QUEST-2) (NCT01290679)
Participants	391 participants Location**:** 14 countries in Europe, North America, and South America **Inclusion criteria:** age ≥ 18 years. Chronic hepatitis C infection. HCV genotype 1. HCV RNA level at screening > 100,000 IU/mL. Treatment-naive. An ultrasound performed within 6 months of enrolment showing no signs of HCC in participants with cirrhosis. **Exclusion criteria:** hepatic decompensation. Any non-HCV-related liver disease. HIV or HBV co-infection. Non-genotype 1 HCV infection. Significant laboratory abnormalities. Any other active disease. Male or female participants who had, or were planning to conceive. **Simeprevir group:** 257 participants Sex: 140 men, 117 women Median age: 46 years (range 18-73) Race: 237 white (92%), 16 black or African American (6%), 2 Asian (< 1%), and 2 other (< 1%) HCV genotype 1a: 105 (41%), HCV genotype 1b: 150 (58%), other HCV genotype: 2 (< 1%) IL28B genotype CC: 75 (29%), IL28B genotype CT: 142 (55%), IL28B genotype TT: 40 (16%) METAVIR score F0-F1: 130 (52%), METAVIR score F2: 65 (26%), METAVIR score F3: 36 (15%), METAVIR score F4: 17 (7%) HCV RNA > 800,000 IU/mL, n(%): 199(77). **Placebo group:** 134 participants Sex: 77 men, 57 women Median age: 47 years (range 18-73) Race: 123 white (92%), 10 black or African-American (10%), 1 Asian (< 1%), and 0 other HCV genotype 1a: 54 (41%), HCV genotype 1b: 77 (58%), other HCV genotype: 2 (2%) IL28B genotype CC: 42 (31%), IL28B genotype CT: 71 (53%), IL28B genotype TT: 21 (16%) METAVIR score, n(%): METAVIR score F0-F1: 60 (45%), METAVIR score F2: 42 (31%), METAVIR score F3: 17 (13%), METAVIR score F4: 15 (11%) HCV RNA > 800,000 IU/mL, n(%): 98(73).
Interventions	**Experimental group:** oral simeprevir 150 mg once daily for 12 weeks. **Control group:** oral placebo 150 mg once daily for 12 weeks. **Co-interventions:** Experimental group: peg-IFN α-2a 180 µg subcutaneously once weekly or peg-IFN α-2b 1.5 µg/kg body weight subcutaneously once weekly and oral weight-based RBV 1000 mg to 1200 mg in 2 divided daily doses (1000 mg if body weight < 75 kg; 1200 mg if body weight ≥ 75 kg) for 24-48 weeks Control group: peg-IFN α-2a 180 µg subcutaneously once weekly or peg-IFN α-2b 1.5 µg/kg body weight subcutaneously once weekly and oral weight-based RBV 1000 to 1200 mg in 2 divided daily doses (1000 mg if body weight < 75 kg; 1200 mg if body weight ≥75 kg) for 48 weeks.

Manns 2014a *(Continued)*

Outcomes	**Primary outcome:** proportion of participants achieving SVR12 (HCV RNA < 25 IU/mL undetectable at end of treatment and < 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment). **Secondary outcomes:** proportion of participants meeting criteria for response-guided therapy to complete treatment at week 24. RVA (HCV RNA < 25 IU/mL undetectable at week 4). Activity, safety, and tolerability of simeprevir in the 2 subpopulations of participants who were given peg-IFN α-2a or 2b. On-treatment failure (detectable HCV RNA at end of treatment). Incidence of viral relapse (HCV RNA ≥ 25 IU/mL during follow-up or at the time of SVR assessments in participants with undetectable levels at end of treatment). Incidence of AEs. Incidence of laboratory abnormalities. Quality-of-life measures. SVR at 24 weeks after the planned end of treatment. Assessment of depression severity. Assessment of health status. Assessment of polymorphisms (HCV NS3 protease domain) at baseline and their correlation with efficacy of simeprevir plus peg-IFN and RBV.
Notes	We emailed Manns and colleagues on 26 April 2016 for additional information blinding of outcome assessors but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated randomisation schedule that was prepared by or under the supervision of the sponsor before the study was used"
Allocation concealment (selection bias)	Low risk	Concealment of allocation was obtained by using an interactive web-based or voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors stated that "patients, study personnel, and the sponsor were masked to the treatment group assignment", the blinding method was not adequately described. A matched placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not mentioned if the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for discontinuation were clearly reported on
Selective reporting (reporting bias)	Low risk	Protocol was available. All pre-specified study outcomes were reported on
Vested-interest bias	Unclear risk	"The sponsor (Janssen Infectious Diseases-Diagnostics) was directly involved in trial design, data analyses and interpretation, and writing and reviewing the manuscript."
Other bias	Low risk	The trial seems to be free of other potential sources of bias

Marcellin 2013a

Methods	Randomised clinical trial
Participants	20 participants **Inclusion criteria:** treatment-naive for chronic hepatitis C

Marcellin 2013a *(Continued)*

	Countries: France, Moldova, Romania, USA
Interventions	**Experimental group:** oral ALS-2200 200 mg once daily for 7 days **Control group:** placebo for 7 days
Outcomes	Safety assessment, HCV RNA
Notes	We emailed Marcellin and colleagues on 27 April 2016 for additional information but reply not received yet. Ongoing study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Safety assessment was not properly described (NCT01356160)
Vested-interest bias	Unclear risk	Not described
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Marcellin 2013b

Methods	Randomised clinical trial
Participants	351 participants **Countries:** France, Germany, Poland, and USA **Inclusion criteria:** treatment-naive non-cirrhotic genotype 1 infected HCV participants **Exclusion criteria:** not described

Marcellin 2013b *(Continued)*

Interventions	**Experimental group:** GS-9451 (200 mg) once daily (those who achieved an extended very rapid virological response (defined as HCV RNA < LLOQ at Weeks 2 and 4 that remained undetectable through week 8) were randomised to stop treatment at either Week 12 or Week 24) **Control group:** no intervention **Co-intervention:** GS-5885 (30mg once a day) + peg (180 mg/week) + RBV (1000 mg–1200 mg/day)
Outcomes	Adverse events, SVR
Notes	We emailed Marcellin and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Safety assessment was not properly described (NCT01356160)
Vested-interest bias	Unclear risk	Not described
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

MATTERHORN 2015a1

Methods	Randomised, open-label, parallel-group trial (ClinicalTrials.gov: NCT01331850)
Participants	381 participants, randomised: 152 prior partial responders (Cohort A) and 229 prior null responders (cohort B) **Sex:** 111 men, 40 women (Cohort A) **Mean age:** 49.4 years **Countries:** Australia, Austria, Brazil, Canada, France, Germany, Italy, Mexico, Poland, Spain, UK, and USA.

MATTERHORN 2015a1 *(Continued)*

	Inclusion criteria: non-cirrhotic adults with HCV genotype 1a or 1b infection, a baseline HCV RNA level P50,000 IU/mL and evidence of prior peg-IFN α-2a/RBV treatment failure. The prior course of treatment must have been discontinued > 12 weeks prior to enrolment, must have comprised at least 12 weeks of therapy with approved doses of peg-IFNα/RBV and participants must have taken a minimum of approximately 80% of the prescribed doses. Prior treatment failure must have been due to either a partial response (> log10 reduction in HCV RNA at week 12, without achieving an undetectable HCV RNA level by the end of treatment), or a null response (< 2 log10 reduction in HCV RNA at week 12). Absence of cirrhosis must have been documented within 24 months of receiving the first dose of study drug either by liver biopsy (Knodell, METAVIR, Batts & Ludwig fibrosis score 63, or Ishak score 64) or, alternatively, by transient elastography (< 14.5 kPa). Participants with a previous liver biopsy were required to have a platelet count > 90 /nL and those with a transient elastography result were required to have a platelet count of 140–400 /nL **Exclusion criteria:** participants were excluded if they were co-infected with HBV or HIV, had liver disease attributed to a cause other than HCV infection, had previously received a DAA agent or had a serious concomitant chronic illness.
Interventions	Participants were grouped according to their prior treatment response (A: partial responders; B: null responders) and were randomised (1:1:1) within each cohort to 1 of 3 treatment arms, stratified by HCV genotype 1 subtype and host IL28B genotype. Participants who received at least 1 dose of study medication: 151 prior partial responders (Cohort A) and 228 prior null responders (cohort B). **Experimental group A1:** oral mericitabine 1000 mg twice a day for 24 weeks. **Control group A2:** peg-IFNα-2a 180 µg once weekly for 24 weeks. **Experimental group A3:** oral mericitabine 1000 mg twice a day for 24 weeks + peg-IFN α-2a 180 µg once weekly for 24 weeks. 24 weeks of peg-IFNα-2a/RBV. **Co-intervention:** oral danoprevir/r 100/100 mg twice daily (twice a day) for 24 weeks + oral RBV 1000 mg (body weight < 75 kg) or 1200 mg (P75 kg) daily for 24 weeks (group A1,A2,A3,)
Outcomes	Proportion of participants with sustained virological response (SVR24), with SAE, AEs, mortality.
Notes	Due to the parallel design only group A1 and group A3 had an adequate control group (A2), Group B1, B2 and B3 were excluded from the analysis This analysis A1 vs. control.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was centralised and the computer-generated randomisation list was maintained
Allocation concealment (selection bias)	Low risk	Randomisation list was maintained by Perceptive Informatics (Waltham, MA, USA). "Study sites were informed of participant treatment assignments by an interactive voice/web response system."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study

MATTERHORN 2015a1 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 participants had incomplete data.
Selective reporting (reporting bias)	High risk	The authors did not report on "Change in danoprevir plasma concentration" as was prespecified in their protocol
Vested-interest bias	High risk	This study was funded by F Hoffmann-La Roche Ltd
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

MATTERHORN 2015a2

Methods	For characteristics see MATTERHORN 2015a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was centralised and the computer-generated randomisation list was maintained
Allocation concealment (selection bias)	Unclear risk	Randomisation list was maintained by Perceptive Informatics (Waltham, MA, USA). Study sites were informed of participant treatment assignments by an interactive voice/web response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 2 participants had incomplete data.
Selective reporting (reporting bias)	High risk	The authors did not report on "Change in danoprevir plasma concentration" as was prespecified in their protocol
Vested-interest bias	High risk	This study was funded by F Hoffmann-La Roche Ltd
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

McHutchison 2009

Methods	A phase IIb, randomised, double-blind, multicenter, parallel-group trial (PROVE-1)(NCT00336479)
Participants	250 participants **Sex:** 157 men, 93 women **Country:** USA **Inclusion criteria:** age between 18 and 65 years. Chronic hepatitis C infection. HCV genotype 1. Treatment-naive. Seronegative for hepatitis B surface. antigen and antibodies against HIV-1 and HIV-2. Absolute neutrophil count ≥ 1500 cells/mm^3. Platelet count ≥ 90,000 cells/mm^3. Normal haemoglobin level **Exclusion criteria:** decompensated liver disease. Another cause of clinically significant liver disease. HCC. Histologic evidence of cirrhosis (on liver biopsy, which was required within 2 years before the study). **Group 1:** 79 participants (T12PR24) Median age: 49 years (range 21-61) Sex: 54 men, 25 women Race: 60 white (76%), 7 black (9%), 1 Asian (1%), 9 Hispanic (11%), and 2 other (3%) HCV genotype, n(%): 1a: 53(67), 1b: 17(22), intermediate: 9(11) HCV RNA ≥ 800,000 IU/mL, n(%): 66(84) Fibrosis, n(%): none or minimal: 24(30), portal: 41(52), bridging: 14(18) **Group 2:** 79 participants (T12PR48) Median age: 50 years (range 26-61) Sex: 48 men, 31 women Race: 60 white (76%), 8 black (10%), 3 Asian (4%), 7 Hispanic (9%), and 1 other (1%) HCV genotype, n(%): 1a: 48(61), 1b: 27(34), intermediate: 4(5) HCV RNA ≥ 800,000 IU/mL, n(%): 68(86) Fibrosis, n(%): none or minimal: 34(43), portal: 31(39), bridging: 14(18) **Group 3:** 17 participants (T12PR12) Median age: 49 years (range 34-63) Sex: 12 men, 5 women Race: 13 white (76%), 3 black (18%), 0 Asian, 1 Hispanic (6%), and 0 other HCV genotype, n(%): 1a: 9(53), 1b: 6(35), intermediate: 2(12) HCV RNA ≥800,000 IU/mL, n(%): 15(88) Fibrosis, n(%): none or minimal: 4(24), portal: 9(53), bridging: 4(24) **Group 4:** 75 participants (PR48) Median age: 49 years (range 24-59) Sex: 43 men, 32 women

McHutchison 2009 *(Continued)*

	Race: 59 white (79%), 9 black (12%), 0 Asian, 6 Hispanic (8%), and 1 other (1%) HCV genotype, n(%): 1a: 50(67), 1b: 20(27), intermediate: 5(7) HCV RNA ≥ 800,000 IU/mL, n(%): 69(92) Fibrosis, n(%): none or minimal: 19(25), portal: 37(49), bridging: 19(25).
Interventions	**Experimental group:** 1, 2, and 3: oral telaprevir given as a single initial dose of 1250 mg, followed by 750 mg every 8 h for 12 weeks (T12). **Control group:** 4: Placebo for 12 weeks. **Co-interventions:** 1: peg-IFN α-2a 180 µg subcutaneously once weekly plus oral weight-based RBV 1000 mg-1200 mg daily in 2 divided doses for 24 weeks (PR24). 2 and 4: peg-IFN α-2a 180 µg subcutaneously once weekly plus oral weight-based RBV 1000 mg-1200 mg daily in 2 divided doses for 48 weeks (PR48). 3: peg-IFN α-2a 180 µg subcutaneously once weekly plus oral weight-based RBV 1000 mg-1200 mg daily in 2 divided doses for 12 weeks (PR12).
Outcomes	**Primary outcome:** proportion of participants with undetectable HCV RNA at 24 weeks after completion of study drug dosing (SVR24). **Secondary outcomes:** proportion of participants with SVR at 12 weeks after completion of study drug dosing. Number of participants with AEs and SAE. Number of participants with viral relapse. Maximum, minimum, and average plasma concentration of telaprevir.
Notes	We emailed McHutchinson and colleagues on 27 April 2016 for additional information on random sequence generation, allocation concealment and SAE but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Not enough information was provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A telaprevir-matched placebo given in the same manner was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Data management and interim analyses were performed by the Duke Clinical Research Institute. An independent data-monitoring committee reviewed the results of all interim analyses"
Incomplete outcome data (attrition bias) All outcomes	High risk	The number of participants who discontinued treatment was clearly stated, but reasons were not mentioned. Up to 36% of participants in a group discontinued study treatment

McHutchison 2009 *(Continued)*

Selective reporting (reporting bias)	Low risk	The protocol was available and all pre-specified outcomes were reported on
Vested-interest bias	High risk	The sponsor (Vertex Pharmaceuticals) was directly involved in trial design and protocol development
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

McHutchison 2010

Methods	A phase II, randomised, partially placebo-controlled, partially double-blind, parallel-group trial (PROVE-3)(NCT00420784)
Participants	453 participants **Sex:** 306 men, 147 women **Mean age:** 51 years **Inclusion criteria:** age between 18 and 70 years, chronic hepatitis C infection, HCV genotype 1, previously treated, but without achieving SVR. Seronegative for hepatitis B surface antigen and antibodies against HIV-1 and HIV-2, absolute neutrophil count ≥ 1500 cells/mm^3, platelet count ≥ 100,000 cell/mm^3, normal bilirubin values. **Exclusion criteria:** decompensated liver disease, HCC, other clinically significant liver disease. **Country:** Canada, Germany, the Netherlands, Puerto Rico and USA. **Group 1:** 115 participants (T12PR24) Sex: 78 men, 37 women Median age: 51 years (range 22-65) Race, n(%): white: 103(90), black: 9(8), Asian: 2(2), other: 1(1) HCV genotype, n(%): 1a: 69(60), 1b: 33(29), unknown: 13(11) HCV RNA ≥ 800,000 IU/mL, n(%): 106(92) Stage of fibrosis or cirrhosis, n(%): none or minimal: 26(23), portal fibrosis: 44(38), bridging fibrosis: 26(23), cirrhosis. 19(17) **Group 2:** 113 participants (T24PR48) Sex: 80 men, 33 women Median age: 52 years (range 31-66) Race, n(%): white: 99(88), black: 11(10), Asian: 0, other: 3(3) HCV genotype, n(%): 1a: 61(54), 1b: 42(37), unknown: 10(9) HCV RNA ≥ 800,000 IU/mL, n(%): 104(92) Stage of fibrosis or cirrhosis, n(%): None or minimal: 20(18), portal fibrosis: 40(35), bridging fibrosis: 33(29), cirrhosis. 20(18) **Group 3:** 111 participants (T24PR24) Sex: 72 men, 39 women

McHutchison 2010 *(Continued)*

	Median age: 53 years (range 19-69) Race, n(%): white: 100(90), black: 10(9), Asian: 1(1), other: 0. HCV genotype, n(%): 1a: 64(58), 1b: 36(32), unknown: 11(10) HCV RNA ≥ 800,000 IU/mL, n(%): 104(94) Stage of fibrosis or cirrhosis, n(%): none or minimal: 17(15), portal fibrosis: 40(36), bridging fibrosis: 32(29), cirrhosis. 22(20) **Group 4:** 114 participants (PR48) Sex: 76 men, 38 women Median age: 50 years (range 18-65) Race, n(%): white: 100(88), black: 10(9), Asian: 2(2), other: 2(2) HCV genotype, n(%): 1a: 71(62), 1b: 34(30), unknown: 9(8) HCV RNA ≥ 800,000 IU/mL, n(%): 104(91) Stage of fibrosis or cirrhosis, n(%): none or minimal: 33(29), portal fibrosis: 37(32), bridging fibrosis: 31(27), cirrhosis 13(11).
Interventions	**Experimental group:** 1: oral telaprevir given in a single initial dose of 1125 mg, followed by 750 mg every 8 h for 12 weeks (T12). 2 and 3: oral telaprevir given in a single initial dose of 1125 mg, followed by 750 mg every 8 h for 24 weeks (T24). **Control group:** 1: placebo from Week 13 to Week 24. 4: placebo for 24 weeks. **Co-intervention:** 1 and 3: peg-IFN α-2a 180 µg subcutaneously once weekly plus oral weight-based RBV 1000 mg to 1200 mg daily in 2 divided doses for 24 weeks (PR24). 2 and 4: peg-IFN α-2a 180 µg subcutaneously once weekly plus oral weight-based RBV 1000 mg to 1200 mg daily in 2 divided doses for 48 weeks (PR48).
Outcomes	**Primary outcome:** SVR defined as undetectable HCV RNA level 24 weeks after the last dose of study drugs. **Secondary outcome measures:** proportion of participants with undetectable HCV RNA at completion of study drug dosing. Number of participants with AEs and SAE. Number of participants with viral relapse. Maximum, minimum, and average plasma concentration of telaprevir.
Notes	We emailed McHutchinson and colleagues on 27 April 2016 for additional information on generation of random sequence, allocation concealment, description of blinding but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not specified

McHutchison 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information was provided on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The method of blinding was insufficiently described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Data management and interim analyses were conducted by the Duke Clinical Research Institute, without revealing the unblinded data"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for discontinuation of treatment were clearly reported. Most participants discontinued treatment due to meeting pre-specified stopping rules
Selective reporting (reporting bias)	Low risk	Protocol was available and all pre-specified outcomes were reported on
Vested-interest bias	High risk	The sponsor (Vertex Pharmaceuticals) was directly involved in trial design, protocol development, study co-ordination, drafting and reviewing the manuscript
Other bias	Low risk	The trial appeared to be free of other potential sources of bias

Mostafa 2015

Methods	Randomised clinical trial
Participants	40 participants **Inclusion criteria:** previously untreated adults with chronic hepatitis C genotype 4 infection. **Country:** Egypt
Interventions	**Experimental group:** 44 weeks of boceprevir 800 mg 3 times daily. **Control group:** no intervention. **Co-intervention:** peg α-2b 1.5 lg/kg once per week subcutaneously plus weight-based dosing RBV 15 mg/kg/day (800 mg-1400 mg/day) for 48 weeks.
Outcomes	Proportion of participants who achieved early response
Notes	We emailed Mostafa and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Mostafa 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	The trial is not finished according to ClinicalTrials.gov, therefore not all data might have been collected yet
Vested-interest bias	Low risk	Trial was funded by a non-profit organisation (Theodor Bilharz Research Institute)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Muir 2014

Methods	Randomised clinical trial
Participants	30 participants **Sex:** 18 men, 12 women **Mean age:** 51.7 years **Inclusion criteria:** adults with chronic hepatitis C, HCV RNA > 10,000 IU/mL at screening, treatment-naive participants defined as participants who have never received peg-IFN, RBV, or a DAA agent for the treatment of chronic HCV infection and a liver biopsy within the last 3 years without evidence of cirrhosis. **Exclusion criteria:** BMI > 36.0, pregnant or nursing (lactating) women, confirmed by a positive human chorionic gonadotropin laboratory test or women contemplating pregnancy, participation in any interventional clinical trial within 35 days prior to first study medication dose administration on Day 1, known HIV-1 or HIV-2 infection/serology and/or positive Hepatitis B surface antigen, use of dietary supplements, grapefruit juice, herbal supplements, cytochrome P2C8 substrates, cytochrome P3A4 inducers and inhibitors, P-glycoprotein inducers and substrates, organic anion transporting polypeptides inhibitors and substrates, and potent inducers of other cytochrome P enzymes within 14 days prior to dosing through 7 days following completion of study meds. Clinically significant laboratory abnormality at screening (specified in protocol), other forms of liver disease, history of severe or uncontrolled psychiatric disease, history of malignancy of any organ system, treated or untreated within the past 5 years, history of major organ transplantation, use of bone marrow colony-stimulating factor agents within 3 months prior to baseline, history of seizure disorder requiring ongoing medical therapy, history of known coagulopathy including haemophilia, history of haemoglobinopathy, including sickle cell anemia and thalassaemia, history of immunologically-mediated disease (specified in protocol), history of clinical evidence of significant chronic cardiac disease (specified in protocol), ECG with any clinically significant abnormality, structural or functional cardiac abnormalities (specified in protocol), history of chronic obstructive pulmonary disease, emphysema, or other chronic lung disease, participants currently abusing amphetamines, cocaine or opiates, or with ongoing alcohol abuse in the judgement of the investigator.
Interventions	**Experimental group:**

Muir 2014 *(Continued)*

	Arm 1: sovaprevir 200 mg once a day + ACH-3102 150 mg loading dose on Day 1 followed by 50 mg once a day + RBV weight-based 1000 mg-1200 mg once a day for 12 weeks. Arm 2: sovaprevir 400 mg once a day + ACH-3102 150 mg loading dose on Day 1 followed by 50 mg once a day + RBV weight-based 1000 mg-1200 mg once a day for 12 weeks. **Control group:** placebo for sovaprevir capsule once a day + placebo for ACH-3102 150 mg loading dose on Day 1 followed by 50 mg capsule once a day + placebo for weight-based RBV once a day for 12 weeks.
Outcomes	Safety, SVR4 (only experimental group).
Notes	We contacted the trial authors about random sequence generation, allocation, participants completing the study, blinding, number of deaths, SVR24.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded but there was no description of the placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blinded but there was no description of the placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were above 5% dropouts (2/30) and it was unclear how the trial dealt with missing data
Selective reporting (reporting bias)	High risk	The original secondary outcomes were later removed (NCT01849562)
Vested-interest bias	High risk	The trial was sponsored by a company with a given interest in a result (Achillion Pharmaceuticals)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nelson 2011

Methods	Phase IIb, randomised, dose-ranging, parallel-design trial (PROTON)
Participants	121 participants **Country:** not stated **Inclusion criteria:** chronic hepatitis C, genotype 1, treatment-naive participants.

Nelson 2011 *(Continued)*

	Exclusion criteria: cirrhosis.
Interventions	**Experimental group:** Group 1: 95 participants: PSI-7977 200 or 400 mg daily for 12 weeks. **Control group:** Group 2: 26 participants: placebo for 12 weeks. **Co-intervention** in both groups: peg-IFN α-2a for 24-48 weeks in a response-guided regimen. RBV for 24-48 weeks in a response-guided regimen.
Outcomes	Not clearly stated.
Notes	We contacted the trial authors about whole risk of bias assessment, male:female ratio, SVR results and AEs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Use of placebo suggests blinding, but method not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to assess whether missing data were likely to induce bias on the results
Selective reporting (reporting bias)	Unclear risk	No protocol available. Not enough information given
Vested-interest bias	Unclear risk	It was uncertain how the trial was sponsored
Other bias	Low risk	The trial may or may not have been free of other domains that could put it at risk of bias

Nelson 2012a1

Methods	Randomised clinical trial
Participants	516 adult participants **Sex:** 311 men, 193 women (analysed only) **Mean age:** 46.5 years

Nelson 2012a1 *(Continued)*

	Inclusion criteria: participants aged 18-65 years with HCV genotype l infection who had never received treatment for chronic hepatitis C were eligible for the trial. Chronic hepatitis C was defined as the presence of anti-HCV antibodies and an HCV RNA titer ≥ 50,000 IU/mL in serum (COBAS® Ampliprep/COBAS® TaqMan® HCV test; detection limit 15 IU/mL, Roche Diagnostics, Indianapolis, USA) with a liver biopsy obtained within the previous 24 months (36 months in participants with cirrhosis or incomplete/transition to cirrhosis) consistent with chronic hepatitis C. HCV genotype 1 infection was confirmed by a molecular assay (Versant HCV Genotyping 2.0 Assay (LiPA), Bayer Diagnostics And Innogenetics, NY, USA). Participants with advanced fibrosis according to a biopsy obtained within the previous 36 months were required to have compensated liver disease (Child–Pugh grade A), a serum α- fetoprotein level < 100 ng/mL, and no evidence of HCC on an ultrasound, computerised tomography, or magnetic resonance imaging scan performed within the previous 2 months. **Exclusion criteria:** participants were not eligible if they were infected with any HCV genotype other than genotype 1 or had serological evidence of infection with HBV or HIV. Participants were also excluded if they had a BMI < 18 kg/ m2 or ≥ 36 kg/m2, an absolute neutrophil count < 2 × 109 cells/L, a platelet count < 90 × 109 cells/L, a hemoglobin concentration < 120 g/L in women or < 130 g/L in men (or in participants with risk factors for anemia or in whom anemia would be medically problematic), or a serum creatinine level > 1.5 times the ULN. Use of erythropoietin-stimulating agents or colony-stimulating factors to elevate haematology parameters to facilitate entry into the study was prohibited. Participants who had previously received any IFN preparation, RBV (or RBV analog), or any investigational HCV protease or polymerase inhibitor were excluded, as were those with a history or evidence of a chronic liver disease other than chronic hepatitis C, a current or past history of chronic disease (including severe psychiatric or pulmonary disease), or a history or evidence of a clinically relevant ophthalmological disorder (e.g. cytomegalovirus infection or macular degeneration). Pregnant or breast-feeding women and male partners of pregnant women were ineligible for the trial. Female participants of childbearing potential and male participants with partners of childbearing potential were required to use 2 forms of effective contraception during treatment and after the last dose of RBV in accordance with the locally approved label for RBV.
Interventions	**Expertimental group:** 1. RO4588161 1000 mg orally twice a day for 24 weeks 2. RO4588161 500 mg orally twice a day for 24 weeks 3. RO4588161 500 mg orally twice a day for 24 weeks. Those participants with undetectable HCV RNA in serum (< 15 IU/mL) at week 4 and who remained HCV RNA undetectable through week 22 were to stop all treatment at week 24; those participants who did not meet this criterion were to continue the 3-drug combination for a further 24 weeks to complete a total treatment duration of 48 weeks. 4. RO4588161 1500 mg orally twice a day for 24 weeks 5. RO4588161 1000 mg orally twice a day for 24 weeks 6. RO4588161 500 mg orally twice a day for 24 weeks **Control group:** placebo. **Co-interventions:** Copegus 1000 mg/1200 mg orally daily for 48 weeks. Peg 180 µgsubcutaneously weekly for 24 weeks (groups 1-3 + control). Copegus 1000 mg/1200 mg orally daily for 48 weeks. Peg 90 µg subcutaneously weekly for 24 weeks (groups 4-6 + control).
Outcomes	Safety, antiviral activity, SVR12, relapse.
Notes	The planned treatment duration with balapiravir was reduced from 24 to 12 weeks due to safety concerns. We emailed Nelson and colleagues on 06 June 2016 for additional information on incomplete outcome data and SVR but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement

Nelson 2012a1 *(Continued)*

Random sequence generation (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Allocation concealment (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Blinding of participants and personnel (performance bias) All outcomes	High risk	"All patiants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN α-2a (40KD) and RBV was permanently discontinued"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"All patients were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN α-2a (40KD) and RBV was permanently discontinued"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was more than 5% dropouts and it was unclear how the trial accounted for missing data
Selective reporting (reporting bias)	High risk	Relapse rate was not reported on despite being stated as an outcome in the protocol (NCT 00517439).
Vested-interest bias	High risk	The trial was supported by a company with an interest in a given result (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nelson 2012a2

Methods	For characteristics see Nelson 2012a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Allocation concealment (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers

Nelson 2012a2 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued
Blinding of outcome assessment (detection bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was more than 5% dropouts and it was unclear how the trial accounted for missing data
Selective reporting (reporting bias)	High risk	Relapse rate was not reported on despite being stated as an outcome in the protocol (NCT 00517439).
Vested-interest bias	High risk	The trial was supported by a company with an interest in a given result (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nelson 2012a3

Methods	For characteristics see Nelson 2012a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Allocation concealment (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Blinding of participants and personnel (performance bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued.
Blinding of outcome assessment (detection bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued

Nelson 2012a3 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was more than 5% dropouts and it was unclear how the trial accounted for missing data
Selective reporting (reporting bias)	High risk	Relapse rate was not reported on despite being stated as an outcome in the protocol (NCT 00517439)
Vested-interest bias	High risk	The trial was supported by a company with an interest in a given result (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nelson 2012a4

Methods	For characteristics see Nelson 2012a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Allocation concealment (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Blinding of participants and personnel (performance bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued
Blinding of outcome assessment (detection bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was more than 5% dropouts and it was unclear how the trial accounted for missing data
Selective reporting (reporting bias)	High risk	Relapse rate was not reported on despite being stated as an outcome in the protocol (NCT 00517439).
Vested-interest bias	High risk	The trial was supported by a company with an interest in a given result (Hoffmann-La Roche)

Nelson 2012a4 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nelson 2012a5

Methods	For characteristics see Nelson 2012a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Allocation concealment (selection bias)	Low risk	The computerized randomizsation list was generated by the sponsor, maintained in a central repository accessible only to the randomizsation list managers, and incorporated in double-blind labelling of medication containers
Blinding of participants and personnel (performance bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued.
Blinding of outcome assessment (detection bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was more than 5% dropouts and it was unclear how the trial accounted for missing data
Selective reporting (reporting bias)	High risk	Relapse rate was not reported on despite being stated as an outcome in the protocol (NCT 00517439)
Vested-interest bias	High risk	The trial was supported by a company with an interest in a given result (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nelson 2012a6

Methods	For characteristics see Nelson 2012a1

Nelson 2012a6 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Allocation concealment (selection bias)	Low risk	The computerised randomisation list was generated by the sponsor, maintained in a central repository accessible only to the randomisation list managers, and incorporated in double-blind labelling of medication containers
Blinding of participants and personnel (performance bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued.
Blinding of outcome assessment (detection bias) All outcomes	High risk	All participants were unblinded to their treatment assignment and, among those who received balapiravir and who had a CD4+ count < 200 cells/mm3, treatment with peg-IFN alfa-2a (40KD) and RBV was permanently discontinued.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was more than 5% dropouts and it was unclear how the trial accounted for missing data
Selective reporting (reporting bias)	High risk	Relapse rate was not reported on despite being stated as an outcome in the protocol (NCT 00517439).
Vested-interest bias	High risk	The trial was supported by a company with an interest in a given result (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nelson 2012b

Methods	Randomised clinical trial
Participants	323 adult participants **Inclusion criteria:** chronic HCV infection for at least 6 months prior to baseline (Day 1), liver biopsy results (performed no more than 2 years prior to screening) indicating the absence of cirrhosis, mono-infection with HCV genotype 1a or 1b, HCV treatment-naive, BMI between 18 and 36 kg/m2, creatinine clearance >/= 50 mL/min, participant agreed to use highly effective contraception methods if female of childbearing potential or sexually active male, screening laboratory values within defined thresholds for ALT, AST, leukopenia, neutropenia, anaemia, thrombocytopenia, thyroid stimulating hormone, potassium, magnesium.

Nelson 2012b *(Continued)*

	Exclusion criteria: autoimmune disease, decompensated liver disease or cirrhosis, poorly controlled diabetes mellitus, severe psychiatric illness, severe chronic obstructive pulmonary disease, serological evidence of co-infection with HIV, HBV, or another HCV genotype, suspicion of HCC or other malignancy (with exception of certain skin cancers), history of haemoglobinopathy, known retinal disease. participants who were immunosuppressed, participants with known, current use of amphetamines, cocaine, opiates (i.e. morphine, heroin), methadone, or ongoing alcohol abuse, participants who were on or are expected to be on a potent cytochrome P450 (CYP) 3A4 or Pgp inhibitor, or a QT prolonging medication within 2 weeks of baseline (Day 1) or during the study, participants must have had no history of clinically significant cardiac disease, including a family history of Long QT syndrome, and no relevant ECG abnormalities at screening.
Interventions	**Experimental group 1:** tegobuvir (20 mg twice a day) + GS-9256 (150 mg twice a day). **Experimental group 2:** GS-9256 (150 mg twice a day). **Control group:** placebo. **Co-intervention:** Peg (180 mg/week) + RBV (1000–1400 mg/day).
Outcomes	Safety, SVR12 (not fully reported so could not be used).
Notes	Participants receiving the 4-drug therapy who achieved an extended vRVR were randomised to stop treatment at either Week 16 or Week 24. We contacted the trial authors on 06 June 2016 for additional information allocation sequence generation, blinding, dropouts and how this was handled, primary publication, SAE, death, SVR24, number of participants randomised to each group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double blind but the placebo was not further described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants dropped out
Selective reporting (reporting bias)	High risk	Not all predefined outcomes in the protocol were reported on (viral resistance, SVR24)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Gilead Sciences)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nettles 2010

Methods	Randomised clinical trial
Participants	18 participants **Sex:** 10 men, 8 women **Mean age:** 44 years **Inclusion criteria:** participants chronically infected with hepatitis C virus genotype 1, treatment-naive or treatment non-responders or treatment intolerant; and not co-infected with HIV or HBV, HCV-RNA viral load of ≥ 10*5* IU/mL and had a BMI 18-35 kg/m^2 **Exclusion criteria:** any significant acute or chronic medical illness which was not stable or not controlled with medication and not consistent with HCV infection and major surgery within 4 weeks of study drug administration and any gastrointestinal surgery that could impact the absorption of study drug
Interventions	**Experimental group:** 1. daclatasvir 1 mg 2. daclatasvir 10 mg 3. daclatasvir 100 mg **Control group:** placebo
Outcomes	Pharmacokinetics, antiviral activity, safety.
Notes	We contacted trial authors for additional information on allocation sequence generation and concealment, how was blinding maintained, whether HIV participants included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants dropped out and it was unclear how the trial handled missing data
Selective reporting (reporting bias)	Low risk	All the outcomes stated in the protocol were reported on NCT00546715
Vested-interest bias	Unclear risk	The trial was funded by a company that might have an interest in a given result (Bristol-Myers Squibb)

Nettles 2010 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nettles 2011a1

Methods	Randomised clinical trial
Participants	**Sex:** 25 men, 5 women **Mean age:** 44.3 years **Inclusion criteria:** eligible participants for this study were men and women, ages 18-60 years inclusive, with a BMI of 18-35 kg/m2, who were chronically infected (longer than 6 months) with HCV genotype 1, and who were treatment-naive to IFN and RBV. Additional inclusion criteria were: plasma HCV RNA 100,000 IU/mL; documented FibroTest score of 0.72 and APRI 2, or the absence of cirrhosis based on liver biopsy within 12 months; women of childbearing potential were not to be nursing or pregnant and had to be willing to agree to use double barrier contraception for at least 1 month before dosing, during dosing, and at least 12 weeks after the last dose of study medication. **Exclusion criteria:** participants with prior documented cirrhosis on liver biopsy; previous exposure to a NS5A replication cofactor inhibitor; co-infection with HIV; co-infection with HBV.
Interventions	**Experimental group:** 1. daclatasvir (1 mg) once a day. 2. daclatasvir (10 mg) once a day. 3. daclatasvir (30 mg) once a day. 4. daclatasvir (60 mg) once a day. 5. daclatasvir (100 mg) once a day. 6. daclatasvir (30 mg) twice a day. **Control group:** placebo.
Outcomes	Pharmacokinetics, mortality, SAE, antiviral efficacy
Notes	We contacted the trial authors on 06 June 2016 for additional information on blinding of participants, personnel and outcome assessors, SVR24

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Compute- generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Nettles 2011a1 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant did not complete the study until day 28
Selective reporting (reporting bias)	High risk	There were added multiple secondary outcomes to the original protocol after the trial was conducted (NCT00663208)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Bristol-Myers Squibb)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nettles 2011a2

Methods	For characteristics see Nettles 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant did not complete the study until day 28
Selective reporting (reporting bias)	High risk	There were added multiple secondary outcomes to the original protocol after the trial was conducted (NCT00663208)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Bristol-Myers Squibb)

Nettles 2011a2 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nettles 2011a3

Methods	For characteristics see Nettles 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant did not complete the study until day 28
Selective reporting (reporting bias)	High risk	There were added multiple secondary outcomes to the original protocol after the trial was conducted (NCT00663208)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Bristol-Myers Squibb)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nettles 2011a4

Methods	For characteristics see Nettles 2011a1
Participants	

Nettles 2011a4 *(Continued)*

Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant did not complete the study until day 28
Selective reporting (reporting bias)	High risk	There were added multiple secondary outcomes to the original protocol after the trial was conducted (NCT00663208)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Bristol-Myers Squibb)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nettles 2011a5

Methods	For characteristics see Nettles 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Nettles 2011a5 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant did not complete the study until day 28
Selective reporting (reporting bias)	High risk	There were added multiple secondary outcomes to the original protocol after the trial was conducted (NCT00663208)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Bristol-Myers Squibb)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nettles 2011a6

Methods	For characteristics see Nettles 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded but the placebo was not described in detail

Nettles 2011a6 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant did not complete the study until day 28
Selective reporting (reporting bias)	High risk	There were added multiple secondary outcomes to the original protocol after the trial was conducted (NCT00663208)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Bristol-Myers Squibb)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nishiguchi 2014a1

Methods	Randomised clinical trial
Participants	**Sex:** 13 men, 9 women **Mean age:** 53.9 years **Inclusion criteria:** treatment-naive adults aged 20–70 years, with chronic genotype-1 HCV infection and HCV RNA viral load at screening ≥ 100,000 IU/mL. **Exclusion criteria:** cirrhosis.
Interventions	**Experimental group:** 1: faldaprevir 120 mg once a day (treatment-naive). 2: faldaprevir 240 mg once a day (treatment-naive). **Control group:** placebo. **Co-intervention:** peg-IFN α-2a 180 µg and RBV 600 mg/day (≤ 60 kg), 800 mg/day (> 60 to ≤ 80 kg) or 1000 mg/day (> 80 kg). Both peg-IFN and RBV were for 44 weeks.
Outcomes	Safety, SVR24.
Notes	We emailed Nishiguchi and colleagues on 24 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial used a "pseudo-random number generator and supplied seed number" to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described

Nishiguchi 2014a1 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was only blinded up to week 8
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial was only blinded up to week 8
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was above 5% dropouts and it was unclear how the trial accounted for missing data
Selective reporting (reporting bias)	High risk	The secondary outcomes were changed after the trial was completed (NCT00947349)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Boehringer Ingelheim)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Nishiguchi 2014a2

Methods	For characteristics see Nishiguchi 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial used a "pseudo-random number generator and supplied seed number" to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was only blinded up to week 8
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial was only blinded up to week 8
Incomplete outcome data (attrition bias)	Unclear risk	There was above 5% dropouts and it was unclear how the trial accounted for missing data

Nishiguchi 2014a2 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	The secondary outcomes were changed after the trial was completed (NCT00947349)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Boehringer Ingelheim)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

OPERA 2011a1

Methods	Phase IIa, randomised, placebo-controlled study, parallel-group design (NCT00561353)
Participants	77 participants (Cohort 1 and 2) and 39 participants (Cohort 4) **Countries:** 26 centres in Belgium, France, Germany, the Netherlands, Poland, and the UK **Inclusion criteria:** eligible participants were aged 18–70 years with documented chronic HCV infection (genotype 1; diagnosis > 6 months prior to screening), a plasma HCV RNA ≥ 10,000 IU/mL (COBAS® TaqMan HCV/HPS assay v2.0 (Roche Molecular Systems, Pleasanton, CA, USA)) and a BMI 18–32 kg/m^2. Participants were either treatment-naive, or were non-responders or relapsers to prior IFN/RBV or peg-IFN/RBV therapy who did not discontinue anti-HCV therapy due to AEs. Participants with compensated cirrhosis (up to Child–Pugh A according to standard criteria) were included. Treatment-experienced participants were defined as non-responders or relapsers who had virologically failed prior IFN/RBV or peg-IFN/RBV therapy. Prior non-responders were those who had not achieved a 2 $\log_{10}$ IU/mL decrease in HCV RNA from baseline after 12 weeks of prior IFN-based therapy. Prior relapsers were those who had detectable HCV RNA during follow-up after achieving undetectable HCV RNA at the end of previous treatment. **Exclusion criteria:** other causes of significant liver disease, decompensated cirrhosis, HCC, prolonged Qtc value, platelet count < 90/nl, neutrophile count < 2/nl, bilirubin > 1.5 x ULN, AST or ALT level > 5 x ULN, excessive use of alcohol, positive urinary drug screening, HIV, Hepatitis B, contraindication for treatment with peg-IFN or RBV.
Interventions	The trial included multiple treatment cohorts. Cohort 1 and 2 included treatment-naive participants. Participants in Cohort 4 were treatment-experienced. **Cohort 1, Panel A:** participants were randomised 3:3:2 Experimental group 1A_1: simeprevir 25 mg once daily for 4 weeks. Experimental group 1A_2: simeprevir 75 mg once daily for 4 weeks. Control group 1A: placebo. Co-intervention 1A: peg-IFN α-2a + RBV in week 2-4. **Cohort 1, Panel B:** Participants were randomised 3:3:2 Experimental group 1B_1: simeprevir 25 mg once daily for 4 weeks. Experimental group 1B_2: simeprevir 75 mg once daily for 4 weeks. Control group 1B: placebo. Co-intervention 1B: peg-IFN α-2a + RBV for 4 weeks. **Cohort 2, Panel A:** participants were randomised 3:1

OPERA 2011a1 *(Continued)*

	Experimental group 2A: simeprevir 200 mg once daily for 4 weeks. Control group 2A: placebo. Co-intervention 2A: peg-IFN α-2a + RBV in week 2-4. **Cohort 2, Panel B:** participants were randomised 3:1. Experimental group 2B: simeprevir 200 mg once daily for 4 weeks. Control group 2B: placebo. Co-intervention 2B: peg-IFN α-2a + RBV for 4 weeks. **Cohort 4:** participants randomised 1:1:1:1 Experimental group 4_1: simeprevir 75 mg once daily for 4 weeks. Experimental group 4_1: simeprevir 150 mg once daily for 4 weeks. Experimental group 4_1: simeprevir 250 mg once daily for 4 weeks. Control group 4: placebo. Co-intervention 4: peg-IFN α-2a + RBV for 4 weeks. Participants in all cohorts 1, 2 and 4 could receive P/R up to week 48 following the initial 28-day TMC435 treatment period.
Outcomes	AE, SAE, change from baseline in HCV RNA level at day 7, percentage of participants with undetectable HCV RNA at week 4.
Notes	A planned cohort 3 should have investigated simeprevir 400 mg once daily, but was cancelled before participant enrolment. This is cohort 125 mg vs control. We emailed Manns and colleagues on 26 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"Randomisation was achieved using the central interactive web response system, managed by ClinPhone Group Ltd"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blinded and placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants were not included in the intention-to-treat analysis resulting in under 5% with missing data

OPERA 2011a1 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported on
Vested-interest bias	High risk	This study was sponsored by Tibotec Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

OPERA 2011a2

Methods	For characteristics see OPERA 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation was achieved using the central interactive web response system, managed by ClinPhone Group Ltd
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blinded and placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants were not included in the intention-to-treat analysis resulting in under 5% with missing data.
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported on
Vested-interest bias	High risk	This study was sponsored by Tibotec Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

OPERA 2011a3

Methods	For characteristics see OPERA 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation was achieved using the central interactive web response system, managed by ClinPhone Group Ltd
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blinded and placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants were not included in the intention-to-treat analysis resulting in under 5% with missing data.
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported on
Vested-interest bias	High risk	This study was sponsored by Tibotec Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

OPERA 2011a4

Methods	For characteristics see OPERA 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

OPERA 2011a4 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation was achieved using the central interactive web response system, managed by ClinPhone Group Ltd
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blinded and placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants were not included in the intention-to-treat analysis resulting in under 5% with missing data.
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported on
Vested-interest bias	High risk	This study was sponsored by Tibotec Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

OPERA 2011a5

Methods	For characteristics see OPERA 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation was achieved using the central interactive web response system, managed by ClinPhone Group Ltd
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blinded and placebo described as identical

OPERA 2011a5 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants were not included in the intention-to-treat analysis resulting in under 5% with missing data
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported on
Vested-interest bias	High risk	This study was sponsored by Tibotec Pharmaceuticals
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

OPERA 2011a6

Methods	For characteristics see OPERA 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation was achieved using the central interactive web response system, managed by ClinPhone Group Ltd
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blinded and placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 5 participants were not included in the intention-to-treat analysis resulting in under 5% with missing data.
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol were reported on
Vested-interest bias	High risk	This study was sponsored by Tibotec Pharmaceuticals

OPERA 2011a6 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pasquinelli 2012a1

Methods	Randomised clinical trial
Participants	**Sex:** 18 men, 6 women **Mean age:** 48 years **Inclusion criteria:** eligible participants with chronic HCV infection were men or women aged 18-60 years with a BMI of 18-35 kg/m2 and chronic infection with HCV genotype 1, either treatment-naive, treatment nonresponders (including relapsers), or treatment intolerant. Additional inclusion criteria were plasma HCV RNA levels of 100,000 IU/mL, a documented FibroTest score of 0.72 or 0.59, and an AST platelet ratio index of 2 or the absence of cirrhosis based on liver biopsy within 12 months **Exclusion criteria:** main exclusion criteria included previous exposure to another NS3 protease inhibitor, co-infection with HIV or HBV, or being women of childbearing potential
Interventions	**Experimental group:** 1. 10 mg single dose 2. 50 mg single dose 3. 200 mg single dose 4. 600 mg single dose **Control group:** placebo every 12 h
Outcomes	Antiviral activity, safety, pharmacokinetics
Notes	We emailed Pasquinelli and colleagues on 06 June 2016 for additional information on description of the placebo, were outcome assessors blinded, who experienced a SAE, how was missing data handled, SVR24 data.but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	An interactive voice-response system was used to assign a unique participant number
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial is described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	There were no dropouts

Pasquinelli 2012a1 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The outcomes reported in the protocol are reported (NCT00559247)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Bristol-Myers Squibb)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pasquinelli 2012a2

Methods	For characteristics see Pasquinelli 2012a1	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	An interactive voice-response system was used to assign a unique participant number
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial is described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were above 5% dropouts and it was unclear how the trial handled missing data
Selective reporting (reporting bias)	Low risk	The outcomes reported in the protocol are reported (NCT00722358)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Bristol-Myers Squibb)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pearlman 2014

Methods	Randomised clinical trial
Participants	101 participants were randomised to either triple (n = 49) or to double therapy (n = 52) **Sex:** 63 men, 38 women **Mean age:** 53 years **Inclusion criteria:** treatment-naive, infected with genotype 1 HCV, and had low viral load at baseline (< 600,000 IU/mL). Participants were 18 years of age or older and had a liver biopsy in the past 2 years consistent with chronic hepatitis. Before randomisation, participants had been rapid virologic responders to 4 weeks of peg-IFN α-2b. **Exclusion criteria:** cirrhosis participants. HCV/HIV co-infection; HCV genotype other than 1; biopsy-proven or strongly suspected clinical cirrhosis; other causes of liver disease, including co-infection with hepatitis B; creatinine clearance < 50 mL/min (modification of diet in renal disease equation); platelet count < 80 3 109/L; neutrophil count < 1.5 3 109/L; haemoglobin concentration < 13 g/dL and 12 g/dL in men and women, respectively; coexisting uncontrolled psychiatric or cardiopulmonary disorders; haemoglobinopathy; sarcoidosis; malignant neoplasm; receipt of immunosuppressive or immunomodulatory therapy in the previous 6 months; pregnancy; and men whose partners were pregnant or unwilling to use contraception during the study period. Female participants of childbearing age also agreed to avoid systemic contraception if ultimately randomised into the protease inhibitor-containing arm. Participants were also excluded if they imbibed significant amounts of alcohol (> 30 g/day), or if they were active substance abusers in the past 6 months.
Interventions	**Experimental group:** 24 weeks of peg/RBV/BOC (boceprevir 800 mg three times a day) (Group A). **Co-intervention:** 20 weeks of peg/RBV only (Group B).
Outcomes	Side effects, viral response.
Notes	We contacted trial authors for additional information on unpublished results, randomisation, blinding of outcome assessment, allocation concealment, SAEs and AEs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label, no blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4% in group A and 6% in group B, a total of 10% discontinuations

Pearlman 2014 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol not found
Vested-interest bias	High risk	Dr. Pearlman consults, advises, and is on the speakers' bureau for Merck
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pearlman 2015

Methods	Randomised clinical trial
Participants	93 participants **Sex:** 53 men, 29 women (analysed) **Mean age:** 56.5 (analysed) **Country:** USA **Inclusion criteria:** chronic HCV infection. Participants 18 years or older were eligible for enrolment if they had genotype 1a infection and a plasma HCV RNA level greater than 10,000 IU/mL. African American ethnicity was self-identified by participants at screening. All participants either were previously untreated or had shown a prior null response to peg-IFN/RBV as defined by < a 2-log10 decrease at 12 weeks of therapy compared with a baseline value and as verified by laboratory records. Other eligibility criteria included documentation of cirrhosis by means of a liver biopsy (METAVIR stage 4) or a FibroTest (Lab Corp, Burlington, NC) score > 0.75 and an AST:platelet ratio index > 2, with a Child-Turcotte-Pugh score of < 7 at screening (class A). Participants needed to have had an ultrasound performed within 6 months before screening, or by the time of the baseline visit, with no findings suspicious for HCC, and to have an international normalised ratio of ≤ 2.3, a total bilirubin level of < 3 mg/dL, a platelet count of ≥ 50,000 per mL^3, and a serum albumin level > 2.7 g/dL. There were no upper age or BMI limits. Participants with stable, medicated psychiatric disease and methadone maintenance participants also were eligible. **Exclusion criteria:** non–genotype 1a, including genotype 1 infection that could not be subtyped; prior treatment with telaprevir or boceprevir; a history of decompensation or history of Child-Turcotte-Pugh class B or C; co-infection with HIV or HBV; a creatinine clearance of < 50 mL/min (modification of diet in renal disease equation); a haemoglobin concentration < 12 g/dL in men and < 11 g/dL in women; co-existing uncontrolled psychiatric or cardiopulmonary disorders; haemoglobinopathy; sarcoidosis; malignant neoplasm in the past 5 years except localised nonmelanoma skin cancer; receipt of immunosuppressive or immunomodulatory therapy within the previous 6 months; or participants who were either pregnant or planning to be pregnant or were men whose partners were pregnant or unwilling to use contraception during the study period. Participants who had discontinued prior therapy because of an AE were not eligible.
Interventions	**Experimental group:** oral simeprevir (150 mg) once daily for 12 weeks. **Control group:** peg-IFN α-2b (1.5 µg/kg/wk) (Merck, Whitehouse Station, NJ), oral RBV (1000 mg–1200 mg/day, based on body weight < 75 kg or ≥ 75 kg, respectively) for 12 weeks. **Co-intervention:** sofosbuvir (400 mg) once daily for 12 weeks.
Outcomes	Efficacy, quality of life, safety assessment, virological response
Notes	The trial reported it was linked to (NCT021683615) however the NCT number could not be identified on ClinicalTrials.gov. Seperate data from African-American/white was presented

Pearlman 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial was open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Gilead Sciences
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Petry 2011

Methods	Randomised clinical trial
Participants	84 participants **Sex:** 84 men **Inclusion criteria:** 18-65 years old with HCV RNA > 105 IU/L, and genotype-1 or -3 chronic HCV infection without clinical evidence of cirrhosis.
Interventions	**Experimental group:** doses of 50 mg (genotype-1) or 100 mg (genotype-3) to 800 mg MK-5172) for 7 days. **Control group:** placebo.
Outcomes	Plasma HCV RNA, pharmacokinetics.
Notes	NCT00998985

Risk of bias

Bias	Authors' judgement	Support for judgement

Petry 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being placebo-blinded, but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being placebo-blinded, but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	Unclear risk	Not described
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pockros 2008a1

Methods	Randomised clinical trial
Participants	107 adult participants **Sex:** 67 men, 37 women **Mean age:** 47.08 years **Inclusion criteria:** participants were eligible for inclusion if they were aged 18-65 years and had chronic HCV genotype 1 infection with HCV RNA levels 50,000 IU/mL. Only treatment-naive participants were enrolled in the study. Other inclusion criteria included chronic liver disease consistent with chronic HCV infection on biopsy, and compensated liver disease (Child-Turcotte-Pugh grade A). Women of childbearing potential were required to have a negative blood pregnancy test within the 24-h period prior to the first dose of study medication. All fertile participants, male and female, were required to use 2 forms of effective contraception during treatment and for 6 months afterward. **Exclusion criteria:** participants were excluded from the study if they had infection with any HCV genotype other than genotype 1, or an indeterminate or mixed genotype; hepatic cirrhosis (Knodell score of 4, Metavir score of 4, or Ishak modified histological activity index score of 5 or 6) or incomplete/ transition to cirrhosis (Knodell score of 3, Metavir score of 3, or an Ishak modified histological activity index score of 4 with nodules or 3 bridges); a low absolute neutrophil count (1500 cells/mm3); a low platelet count (120,000 cells/mm3); or a low haemoglobin concentration (13 g/dL in women or 14 g/dL in men), HIV, Hepatitis A, Hepatitis B infection.
Interventions	**Experimental group:** 1. RO5024048 1500 mg orally twice a day for 4 weeks. 2. RO5024048 3000 mg orally twice a day for 4 weeks.

Pockros 2008a1 *(Continued)*

	3. RO5024048 1500 mg orally twice a day for 4 weeks and Copegus 1000 mg/1200 mg orally daily. **Control group:** placebo + Copegus 1000 mg/1200 mg orally daily. **Co-intervention:** Pegasys 180 µg subcutaneously weekly for 4 weeks and 44 weeks of standard of care (peg-IFN α-2a (180 µg subcutaneously), RBV (1000 mg orally once a day for those weighing < 75 kg; 1200 mg orally once a day if ≥ 75 kg) for 4 weeks).
Outcomes	Safety, pharmacokinetics, antiviral efficacy.
Notes	We emailed Pockros and colleagues on 06 June 2016 for additional information on allocation sequence generation, allocation concealment, blinding of outcome assessment, how many dropped out but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and care providers were blinded up until week 8. Outcomes were only reported till week 8 and therefore results were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many dropped out and how the trial dealt with missing data
Selective reporting (reporting bias)	Unclear risk	All outcomes stated in the protocol were reported on (NCT00377182)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pockros 2008a2

Methods	For characteristics see Pockros 2008a1
Participants	
Interventions	
Outcomes	

Pockros 2008a2 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and care providers were blinded up until week 8. Outcomes were only reported till week 8 and therefore results were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many dropped out and how the trial dealt with missing data
Selective reporting (reporting bias)	Unclear risk	All outcomes stated in the protocol were reported on (NCT00377182)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pockros 2008a3

Methods	For characteristics see Pockros 2008a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Pockros 2008a3 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and care providers were blinded up until week 8. Outcomes were only reported till week 8 and therefore results were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many dropped out and how the trial dealt with missing data
Selective reporting (reporting bias)	Unclear risk	All outcomes stated in the protocol were reported on (NCT00377182)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Hoffmann-La Roche)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pockros 2009

Methods	Randomised clinical trial
Participants	244 participants **Mean age:** 50 years **Inclusion criteria:** treatment-naive or prior non-responders. **Exclusion criteria:** women who were pregnant or breastfeeding, ALT >/ or = 5 x the ULN, AST >/ or = 5 x the ULN.
Interventions	**Experimental group:** 1. HCV 796 capsules, 500 mg, every 12 h. daily, 48 weeks (treatment-naive). 2. HCV 796 capsules, 500 mg, every 12 h daily, 48 weeks (non-responders). **Control group:** placebo. **Co-intervention:** Peg-Intron subcutaneous injection, weight-based dosing, weekly and Rebetol capsules, weight-based dosing, every 12 h daily for 48 weeks.
Outcomes	Primary outcome complete early virologic response. Secondary outcome rapid virological response.
Notes	We contacted trial authors for addition information on whether HIV participants included, allocation sequence generation and concealment, how was blinding maintained, who was blinded, maximum follow-up, how many participants dropped out, how was missing data handled, SAE, death, SVR24 but reply not received.

Risk of bias

Bias	Authors' judgement	Support for judgement

Pockros 2009 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial is described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of dropouts was not described
Selective reporting (reporting bias)	Unclear risk	The outcome called upon in the protocol was reported (NCT00367887)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (PfizerViroPharma)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pol 2012

Methods	Randomised clinical trial
Participants	48 participants **Sex:** 32 men, 16 women **Mean age:** 51.3 years **Countries:** USA and France. **Inclusion criteria:** chronic HCV genotype 1 infection and were treatment-naive or had < 4 weeks of exposure to RBV or IFN-based therapy. Participants needed to have an HCV RNA concentration of ≥ 10^5 IU/mL and be aged 18-70 years. **Exclusion criteria:** cirrhosis, by liver biopsy within 24 months of baseline, clinically significant comorbidities, and HIV or hepatitis B co-infection.
Interventions	**Experimental group:** oral 3 mg, 10 mg, 60 mg once daily for 48 weeks. **Control group:** placebo. **Co-intervention:** peg-IFN α-2a (180 µg per week) and RBV (1000 mg–1200 mg daily).
Outcomes	HCV RNA, safety assessment, virological response.
Notes	We emailed Pol and colleagues on 27 April 2016 for additional information but reply not received yet.

Pol 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants and personnel were only blinded until week 12
Blinding of outcome assessment (detection bias) All outcomes	High risk	The sponsors, who performed the analyses, were only blinded until week 12
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	High risk	The trial changed outcomes from the protocol
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Pol 2013

Methods	Randomised clinical trial
Participants	239 participants non-cirrhotic genotype 1 HCV participants **Sex:** unknown **Mean age:** unknown **Exclusion criteria:** none specified.
Interventions	**Experimental group:** GS-9451 (200 mg once a day) alone for 16 or 24 weeks (arm 1) or GS-9451 (200 mg once a day) and tegobuvir (30 mg twice a day) 24 weeks (arm 2). **Control group:** placebo. **Co-intervention:** peg (180 mg/week) + RBV (1000 mg–1200 mg/day) up to 48 weeks based on response to therapy.
Outcomes	Very rapid virological response, rapid virological response, SVR, serious adverse events
Notes	The authors were contacted on 06 June 2016 for additional information on allocation sequence generation, blinding, missing data, SVR24, safety, deaths, full publication

Pol 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants had missing data
Selective reporting (reporting bias)	High risk	SVR24 was not reported but was stated in the protocol (NCT01271790)
Vested-interest bias	High risk	The trial was sponsored by a company with an interest in a given outcome (Gilead Sciences)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Poordad 2007

Methods	Randomised clinical trial
Participants	117 treatment-naive participants with chronic hepatitis C **Exclusion criteria:** pregnant, breastfeeding, or co-infected with HBV and/or HIV.
Interventions	**Experimental group:** valopicitabine 200 mg once a day. **Control group:** RBV 1000 mg-1200 mg daily + valopicitabine placebo once a day. **Co-intervention:** peg-IFNα-2a 180 µg weekly.
Outcomes	Pharmacokinetics, antiviral activity, SAE (not reported fully, so we could not use the data).
Notes	We contacted the trial authors on 06 June 2016 for additional information on allocation sequence generation and concealment, maximum follow-up, how many participants dropped out, how was missing data handled, SAE, Death, SVR24, number randomised in each group.

Risk of bias

Bias	Authors' judgement	Support for judgement

Poordad 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Only described as single blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only described as single blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many dropped out
Selective reporting (reporting bias)	Unclear risk	No outcomes were reported in the protocol (NCT00395421)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result: Merck Sharp & Dohme Corp.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Poordad 2011a1

Methods	A phase III, international, randomised, placebo-controlled, parallel-group study (SPRINT-2) (NCT00705432)
Participants	1097 participants **Country**: France, Germany, Italy and USA **Inclusion criteria:** treatment-naive participants, age ≥ 18 years, weight of 40-125 kg, chronic infection with HCV genotype 1, plasma HCV RNA level ≥ 10,000 IU/mL. **Exclusion criteria:** liver disease of other cause, decompensated cirrhosis, renal insufficiency, HIV or hepatitis B infection, pregnancy, current breastfeeding, active cancer. **Group 1:** 363 participants Sex: 206 men, 157 women Mean age ± SD: 49 ± 10 years Race, n (%): white: 296 (82), black: 52 (14), Asian: 9 (2), other: 6 (2) Location, n (%): North America: 254 (70), Europe: 99 (27), Latin America: 10 (3) Weight, mean ± SD (kg): 80 ± 16 HCV subtype, n (%): 1a: 227 (63), 1b: 121 (33), missing data: 15 (4) HCV RNA level, n (%): > 400,000 IU/mL: 337 (93), > 800,000 IU/mL: 308 (85)

Poordad 2011a1 *(Continued)*

	METAVIR fibrosis score, n(%): 0, 1, or 2: 328 (90), 3 or 4: 24 (7), missing data: 11 (3) **Group 2:** 368 participants Sex: 229 men, 139 women Mean age ± SD: 50 ± 9 years Race, n (%): white: 304 (83), black: 52 (14), Asian: 4 (1), other: 8 (2) Location, n (%): North America: 277 (75), Europe: 79 (21), Latin America: 12 (3) Weight, mean ± SD (kg): 82 ± 17 HCV subtype, n (%): 1a: 234 (64), 1b: 124 (34), missing data: 10 (3) HCV RNA level, n (%): > 400,000 IU/mL: 336 (91), > 800,000 IU/mL: 314 (85) METAVIR fibrosis score, n(%): 0, 1, or 2: 319 (87), 3 or 4: 34 (9), missing data: 15 (4) **Group 3:** 366 participants Sex: 221 men, 145 women Mean ± SD: 49 ± 9 years Race, n (%): white: 295 (81), black: 55 (15), Asian: 8 (2), other: 8 (2) Location, n (%): North America: 270 (74), Europe: 86 (23), Latin America: 10 (3) Weight, mean ± SD (kg) = 82 ± 17 HCV subtype, n (%): 1a: 237 (65), 1b: 117 (32), missing data: 12 (3) HCV RNA level, n (%): > 400,000 IU/mL: 341 (93), > 800,000 IU/mL: 313 (86) METAVIR fibrosis score, n (%): 0, 1, or 2: 313 (86), 3 or 4: 42 (11), missing data: 11 (3)
Interventions	**Experimental group:** **Group 2:** oral boceprevir 800 mg thrice-daily in 4 capsules of 200 mg each (to be taken with food and at an interval of 7-9 h between doses) beginning at week 5, for a total of 24 weeks; if HCV RNA levels were undetectable from week 8-24, treatment was considered complete; if HCV RNA levels were detectable between week 8-24 (not including week 24), boceprevir was continued for additional 20 weeks (total of 44 weeks). **Group 3:** oral boceprevir 800 mg thrice-daily in 4 capsules of 200 mg each (to be taken with food and at an interval of 7-9 h between doses) beginning at week 5, for a total of 44 weeks. **Control group:** **1:** a matched placebo thrice-daily beginning at week 5 for 44 weeks. **Co-intervention:** **All groups:** peg-IFN α-2b 1.5 µg/kg body weight subcutaneously once weekly and weight-based oral RBV at a total dose of 600 mg-1400 mg daily in divided doses for 4 weeks (lead-in period). **Groups 1 and 3:** peg-IFN α-2b 1.5 µg/kg body weight subcutaneously once weekly and weight-based oral RBV at a total dose of 600mg-1400 mg daily in divided doses for additional 44 weeks (total of 48 weeks). **Group 2:** peg-IFN α-2b 1.5 µg/kg body weight subcutaneously once weekly and weight-based oral RBV at a total dose of 600 mg-1400 mg daily in divided doses for additional 24 weeks (total of 28 weeks), and those with a detectable HCV RNA level between weeks 8-24 received the same therapy for an additional 20 weeks (total of 48 weeks).

Poordad 2011a1 *(Continued)*

Outcomes	**Primary outcomes:** achievement of SVR, defined as undetectable plasma HCV RNA at week 24 (if a participant was missing follow-up week 24 and had undetectable HCV RNA level at week 12, the participant was considered an SVR). **Secondary outcomes:** achievement of SVR defined as undetectable HCV RNA at week 24 in non-black/African American randomised participants who received at least 1 dose of experimental study drug or placebo. The proportion of participants with EVR (e.g. undetectable HCV RNA at weeks 2, 4, 8, or 12) who achieved SVR. The proportion of participants with undetectable HCV RNA at week 12. The proportion of participants with undetectable HCV RNA at 72 weeks after randomisation.
Notes	Co-intervention in Group 2 was different from Groups 1 and 3. We emailed Poordad and colleagues on 27 April 2016 for additional information about blinding outcome assessors and number of participants experiencing non-serious AEs but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Low risk	Allocation concealment was done through interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	In the trial's protocol it is described that placebo would be matched to boceprevir and would be given in the same manner
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not mentioned if the outcome assessors were blinded, or the extent of blinding was insufficiently described
Incomplete outcome data (attrition bias) All outcomes	High risk	49/1099 (4.5%) participants discontinued the peg-IFN/RBV therapy during the lead-in period. No specific reasons were given. Due to futility at week 24 another 108, 33, and 36 participants in groups 1, 2, and 3, respectively, discontinued treatment. In total 226/1099 (20,5%) of participants discontinued treatment. No other dropouts were stated
Selective reporting (reporting bias)	Low risk	A protocol was published before randomisation began and all outcome results were reported adequately
Vested-interest bias	High risk	The sponsor (Merck) was directly involved in trial's design, managing, analyses, as well as, writing, decision of submission for publication, reviewing and drafting the manuscript
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Poordad 2011a2

Methods	For characteristics see Poordad 2011a1
Participants	

Poordad 2011a2 *(Continued)*

Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Low risk	Allocation concealment was done through interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	In the trial's protocol it is described that placebo would be matched to boceprevir and would be given in the same manner
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not mentioned if the outcome assessors were blinded, or the extent of blinding was insufficiently described
Incomplete outcome data (attrition bias) All outcomes	High risk	49/1099 (4.5%) participants discontinued the peg-IFN+RBV therapy during the lead-in period. No specific reasons were given. Due to futility at week 24 another 108, 33, and 36 participants in groups 1, 2, and 3, respectively, discontinued treatment. In total 226/1099(20,5%) of participants discontinued treatment. No other drop-outs were stated
Selective reporting (reporting bias)	Low risk	A protocol was published before randomisation began and all outcome results were reported adequately
Vested-interest bias	High risk	The sponsor (Merck) was directly involved in trial's design, managing, analyses, as well as, writing, decision of submission for publication, reviewing and drafting the manuscript
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

POSITRON 2013

Methods	Blinded placebo-controlled trial (NCT01542788)
Participants	Randomised: 280 underwent randomisation, and 278 began treatment Experimental group: 209 randomised, 207 treated Control group: 71 randomised, 71 treated **Sex:** 151 men, 127 women **Mean age:** 52 years **Countries:** 63 sites in the USA, Canada, Australia, and New Zealand from March 2012-May 2012. **Inclusion criteria:** eligible participants were cirrhotic or non-cirrhotic adults with HCV genotype 2 or 3 infection, a baseline HCV RNA level > 10,000 IU/mL unwilling or uneligible or intolerant for IFN-treatment. Participants had chronic hepatitis C infection (documented by positive anti-HCV antibody test or

POSITRON 2013 *(Continued)*

	positive HCV RNA, or positive HCV genotyping test ≥ 6 months prior to the Baseline/Day 1 visit; or documented by liver biopsy performed prior to the Baseline/Day 1 visit with evidence of chronic HCV). Participants had a BMI > = 18 kg/m2, a screening ECG without clinically significant abnormalities, no evidence of HCC, no Chronic liver disease of a non-HCV aetiology (e.g. hemochromatosis, Wilson's disease, α1-antitrypsin deficiency, and cholangitis) and no co-infection with HBV or HIV. Participants had no history of significant pulmonary or cardiac disease, or porphyria; no current or prior history of clinical hepatic decompensation (e.g. ascites, jaundice, encephalopathy, or variceal haemorrhage).
Interventions	Randomisation was performed centrally in a 3:1 ratio with stratification according to the presence or absence of cirrhosis. **Experimental group:** oral sofosbuvir 400 mg once daily + RBV (1000 mg daily in participants with a body weight < 75 kg, and 1200 mg daily in participants with a body weight ≥ 75 kg) for 12 weeks. **Control group:** placebo.
Outcomes	Proportion of participants with end-of-treatment response (week12), SVR12, SAE, AEs, mortality.
Notes	We emailed Jacobson and colleagues on 21 April 2016 for additional information on generation of allocation sequence, how many participants dropped out and how the trial handled missing data but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"An Interactive Web Response System (IWRS) will be employed to manage participant randomization and study drug assignment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participant, caregiver, investigator, outcomes assessor were described as being blinded and the placebo was identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The participant, caregiver, investigator, outcomes assessor were described as being blinded and the placebo was identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants dropped out and how the trial handled missing data
Selective reporting (reporting bias)	Low risk	The outcomes stated in the protocol were reported on
Vested-interest bias	High risk	The sponsor collected the data, monitored study conduct, and performed the statistical analysis
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Reddy 2007

Methods	Randomised clinical trial
Participants	40 adult participants **Inclusion criteria:** chronic hepatitis C genotype 1 whose alpha-IFN treatment had failed. **Exclusion criteria:** non-cirrhotic.
Interventions	**Experimental group:** 1. 750 mg once a day R7128 2. 1500 mg once a day R7128 3. 750 mg twice a day R7128 4. 1500 mg twice a day R7128 **Control group:** placebo
Outcomes	SAE, antiviral activity, safety.
Notes	We contacted the trial authors on allocation sequence generation and concealment, maximum follow-up, how many participants dropped out, how was missing data handled, death, SVR24, and number randomised in each group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There was a placebo but it was unclear how well matched the placebo was and who was blinded to it
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants had missing data
Selective reporting (reporting bias)	Unclear risk	No prepublished protocol could be found
Vested-interest bias	Unclear risk	It was unclear how the trial was funded
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Reesink 2006

Methods	Randomised phase I clinical trial
Participants	37 adult participants **Sex:** 22 men, 12 women (analysed) **Mean age:** 47 years **Countries:** Germany, the Netherlands. **Inclusion criteria:** men or women between the ages of 18 and 65 years, with BMI between 18.5 and 29.0 kg/m2 (men) or 18.5 and 32.5 (women). Entry criteria included an HCV RNA level 1 105 IU/mL as measured using the Roche COBAS TaqMan HCV assay (Roche Molecular Diagnostics, Pleasanton, CA) (confirmed by repeat measure of 2 separate samples taken during the screening period), HCV genotype 1 (any subtype), and an ALT concentration 4 times the ULN. **Exclusion criteria:** decompensated liver disease, cirrhosis, and positive screening for hepatitis B surface antigen or anti-HIV 1/2.
Interventions	**Experimental group:** oral 450 mg or 750 mg of VX-950 3 times daily, or 1250 mg twice daily for 14 days. **Control group:** placebo.
Outcomes	Pharmacokinetics, safety assessment, antiviral assessment.
Notes	We emailed Reesink and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded with matching placebo, but it was unclear if the participants and investigators were blinded to results (except HCV RNA)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as double-blinded with matching placebo, but it was unclear if the participants and investigators were blinded to results (except HCV RNA)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% did not complete the trial (3 participants were not included in the analyses)
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Vertex Pharmaceuticals Incorporated
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Reiser 2005

Methods	Randomised clinical trial
Participants	10 adult participants **Sex:** 8 men, 2 women **Mean age:** 34.5 years **Inclusion criteria:** women or men aged 18 years or older with chronic genotype 2 or 3 HCV infection. The line probe assay was used to determine the genotype of the viral infection. A liver biopsy specimen showing changes consistent with chronic HCV infection had to have been performed within the previous 12 months. At screening, the HCV load had to be 50,000 copies/mL serum. **Exclusion criteria:** women were excluded if they were breast-feeding or at risk of pregnancy; men had to use an adequate form of contraception if their partner was of childbearing potential. They were not enrolled if there were other or additional reasons for chronic liver disease, including the presence of other hepatitis-causing viruses and/or a history of alcohol abuse within the previous 12 months and/or evidence of Child's B or C liver disease at screening. No other antiviral or antimicrobial or investigational therapies were allowed during the study (screening, pretreatment, and treatment phases). Participants were excluded if, at screening, their baseline ALT/AST plasma levels exceeded the ULN by more than 5-fold (5 times the ULN) or their total bilirubin or alkaline phosphatase levels were 1.5 times the ULN. Other exclusion criteria included co-infection with HIV, a platelet count 100,000/mm3, a white blood cell count 2000 cells/mm3, any clinically significant laboratory abnormalities, and a positive test result for illicit or nonprescription drugs.
Interventions	**Experimental group:** oral 500 mg of BILN-2061 for 2 days. **Control group:** placebo.
Outcomes	Virological efficacy, pharmacokinetics, safety.
Notes	We emailed Reiser and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	0 participants dropped out

Reiser 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained for all 3 stages, and the ClinicalTrials.gov information was added after completion
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2008

Methods	Randomised clinical trial
Participants	50 adult participants **Inclusion criteria:** chronic hepatitis C genotype 1 who were treatment-naive. **Exclusion criteria:** none reported.
Interventions	**Experimental group:** 1. 500 mg twice a day R7128 for 28 days. 2. 1500 mg twice a day R7128 for 28 days. **Control group:** placebo. **Co-intervention:** 180 µg peg-IFN α-2a and 1000 mg-1200 mg RBV.
Outcomes	Antiviral activity (RVR), SAE, AE.
Notes	We emailed Rodriguez-Torres and colleagues on 06 June 2016 for additional information on allocation sequence generation and concealment, blinding, incomplete outcome data including which groups the 2 participants who were omitted from the analyses were from, how the trial was funded, prepublished protocol, death, SVR but reply not received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A placebo was mentioned but it was unclear who was blinded to the intervention and how well matched the placebo was
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants had missing data

Rodriguez-Torres 2008 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No prepublished protocol could be found
Vested-interest bias	Unclear risk	It was unclear how the trial was funded
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2010

Methods	Randomised clinical trial
Participants	24 participants (first 3 cohorts) **Inclusion criteria:** participants who were 18-65 years of age, had laboratory evidence of HCV infection for 6 months, defined by 1. presence of anti-HCV antibody (genotype 1a and 1b infection), or 2. documented HCV RNA presence by a sensitive and specific assay and 3. histologic evidence of CHC (Fibrosis on a standardised histological grading system), plasma HCV RNA of 100,000 IU/mL, were HIV 1 and HIV2 ab seronegative, BMI ≤ 35 kg/m2 BMI and treatment-naive. **Exclusion criteria:** contraindications to peg-IFN or RBV therapy, have evidence of liver cirrhosis, decompensated liver disease, and Child-Pugh score > 5, have haemoglobinopathies, unstable cardiac disease, history of organ transplant, active malignant disease or uncontrolled Type I or II diabetes.
Interventions	**Experimental group:** 1. 250 mg twice a day for 3 days. 2. 500 mg twice a day for 3 days. 3. 750 mg twice a day for 3 days. 4. 1500 mg once a day for 3 days. **Control group:** placebo **Co-intervention:** peg-IFN α-2a plus RBV were offered from day 4 for up to 48 weeks.
Outcomes	Pharmacokinetics, antiviral activity, AEs.
Notes	We emailed Rodriguez-Torres and colleagues on 06 June 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blind (participant, caregiver, investigator, outcomes assessor) at ClinicalTrials.gov, but it is not clear how well the placebo was matched

Rodriguez-Torres 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as double-blind (participant, caregiver, investigator, outcomes assessor) at ClinicalTrials.gov, but it was not clear how well the placebo was matched
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants had missing data
Selective reporting (reporting bias)	Unclear risk	No prepublished protocol could be found. The outcomes stated at ClinicalTrials.gov were submitted after the start of the trial (NCT00911963)
Vested-interest bias	High risk	The trial was funded by companies that might have an interest in a given result (Vertex Pharmaceuticals Incorporated and ViroChem Pharma)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2011a1

Methods	Randomised clinical trial
Participants	70 adult participants **Inclusion criteria:** chronic hepatitis C genotype 1 who were men and women, 18-65 years of age inclusive (BMI of at least 18kg/m2 not exceeding 36kg/m2), had a diagnosis of chronic HCV by 1 previous PCR result prior to screening, with a positive HCV viral load of at least 100,000 IU/mL at screening measured by quantitative PCR, HCV genotype 1 per central lab testing report, HCV treatment-naive (defined as no prior treatment with IFN, peg-IFN, RBV, or any HCV DAA drugs), liver biopsy consistent with chronic HCV infection but non-cirrhotic as judged by a pathologist (Knodell < 3, Metavir < 2, Ishak < 4, or Batts & Ludwig < 2) within the last 2 years and before Visit 2 (biopsy can be done within screening period), negative urine drug screen for drugs of abuse at screening and Study Day -1 (methadone use allowed), women would have a negative serum βHCG pregnancy test at screening & negative urine dipstick pregnancy test upon entry to clinical unit on Study Day -1, agreement by both women of childbearing potential and men(who have not been surgically sterilised) to practice an acceptable method of birth control. Surgical sterilisation of either female or male partner must have occurred at least 6 months prior to first dose and women must be post-menopausal for 2 years to be considered of non-child-bearing potential. Acceptable contraceptive methods include 1 of the following: oral and implantable hormonal contraceptives by woman at least 3 months prior to the 1st dose of Study Drug, IUD in place at least 6 months prior to first dose, barrier methods either diaphragm or condom with spermicide. (Abstinence is not an acceptable method of birth control, participants who indicate sexual inactivity must agree to utilise birth control in the event of sexual activity), willing and able to complete all study visits and procedures, and able to communicate with the investigator and other personnel, signed informed consent form executed prior to protocol screening assessments. **Exclusion criteria:** advanced liver disease, cirrhosis, or with signs of decompensated liver disease such as variceal bleeding, ascites, hepatic encephalopathy, active jaundice (total bilirubin > 2, or other evidence of decompensated liver disease, co-infection with HBV or HIV (positive test for HBsAg or anti-HIV Ab), acute cardiac ischaemias, unstable heart disease or clinically symptomatic cardiac abnormalities apparent on ECG & PE, or a QTcB interval at Visit 1 of ≥ to 450 ms by Bazette's correction, or personal or family history of Torsades de pointes, use of the following medications concurrently or within the 30 days prior to screening associated with QT prolongation: macrolides, antiarrhythmic agents, azoles, fluoroquinolones, and tricyclic anti-depressants (methadone use allowed), use of immunosuppressive or immune-modulating agents (including corticosteroids and immunosuppressive agents) or presence of an immunologically-mediated autoimmune disease (other than asthma) or history of organ transplantation (inhaled steroids for asthma and topical steroid for minor skin conditions allowed), use of strong CYP3A4-inhibiting protease inhibitors (specifically atazanavir, indinavir, nelfinavir, saquinavir, and ritonavir), strong CYP3A4 inhibitors (specifically clarithromycin, itraconazole, ketocona-

Rodriguez-Torres 2011a1 *(Continued)*

	zole, nefazodone, telithromycin), or strong CYP3A4 inducers (specifically rifampin, efavirenz, etravirine, phenobarbital, phenytoin, and carbamazepine); absolute NEUT count of < 1800 cells/mm3 (or < 1500 cells/mm3 for African Americans), or platelet count < 130,000 cells/mm3, or haemoglobin < 11g/dL for women and < 13g/dL for men, a history of abnormal thyroid function not adequately controlled (defined as TSH levels < 0.8 x LLN or > 1.2 x the ULN), serum creatinine concentration > 1.5 times the ULN, or albumin < 3g/dL, presence or history of severe, or uncontrolled, or hospitalisation-requiring psychiatric disease including severe depression, suicide attempts or any severity of psychosis, any malignancy within the last 5 years other than treated cervical carcinoma in situ or treated basal cell carcinoma with no more than 20% risk of recurrence within 2 years, alcohol abuse (investigator assessment) within the past 2 years or an alcohol use pattern that will interfere with the study conduct, drug abuse (investigator assessment) within the last 6 months with exception of methadone, current lactation or breastfeeding, major surgery within 30 days prior Visit 1, participation in another clinical trial of an investigational drug or device within 6 months prior to visit donation of blood or plasma within 30 days prior to Visit 1.
Interventions	**Experimental group:** 1. 9 mg INX-08189 once a day for 7 days. 2. 25 mg INX-08189 once a day for 7 days. 3. 50 mg + 9 mg INX-08189 once a day for 7 days. 4. 50 mg + 9 mg INX-08189 once a day for 7 days. 5. 9 mg INX-08189 once a day + RBV for 7 days. 6. 25 mg INX-08189 once a day + RBV for 7 days. 7. 100 mg INX-08189 once a day. **Control group:** Control for arm 1-3: placebo. Control for arm 4-6: placebo + RBV.
Outcomes	Adverse events, antiviral activity
Notes	We emailed Rodriguez-Torres and colleagues on 06 June 2016 for additional information on allocation sequence generation and concealment, how blinding was maintained, if outcome assessors were blinded, how many participants dropped out, SAE, death, SVR, male:female, mean age but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	It was unclear how many participants dropped out

Rodriguez-Torres 2011a1 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The outcomes stated in the protocol were reported on (NCT01250366)
Vested-interest bias	High risk	The trial was supported by a company that might have an interest in a given result (Bristol-Myers Squibb)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2011a2

Methods	Randomised clinical trial
Participants	40 adults with chronic hepatitis C genotype 1 who were treatment-naive.
Interventions	**Experimental group:** 1. 100 mg once a day PSI-322938. 2. 200 mg once a day PSI-322938. 3. 300 mg once a day PSI-322938. 4. 100 mg twice a day PSI-322938. **Control group:** placebo
Outcomes	SAE, AE, HCV RNA, HCV mutations.
Notes	We emailed Rodriguez-Torres and colleagues on 06 June 2016 for additional information on allocation sequence generation and concealment, blinding, incomplete outcome data, how the trial was funded, prepublished protocol, death, SVR but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A placebo was mentioned but it was unclear who was blinded to the intervention and how well matched the placebo was
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants had missing data

Rodriguez-Torres 2011a2 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No prepublished protocol could be found
Vested-interest bias	Unclear risk	It was unclear how the trial was funded
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2013

Methods	Randomised clinical trial
Participants	64 participants **Sex:** 43 men, 20 women **Mean age:** 45.1 years **Inclusion criteria:** 64 treatment-naive participants with chronic HCV genotype 1 infection were enrolled (HCV RNA levels P100,000 IU/mL at screening), 18–65 years of age with a BMI of 18–36 kg/m2. Women of childbearing potential were required to use a protocol-approved method of contraception. 1 participant in the sofosbuvir 200 mg arm withdrew consent before receiving the first dose of study medication. **Exclusion criteria:** a liver biopsy within 3 years of dosing was required to exclude cirrhosis. Participants were otherwise in good health, with no significant co-morbidities. Other key exclusion criteria included positive test for hepatitis B surface antigen, anti-hepatitis B core protein IgM antibodies and anti-HIV antibodies. Randomization was stratified by interleukin(IL) 28B status (rs12979860) for CC or CT/TT allele.
Interventions	Participants were randomised in a ratio of active:placebo of 1:1:1:1 **Experimental group:** participants received 1 of 3 once-daily doses of sofosbuvir (100 mg, 200 mg, or 400 mg). **Control group:** placebo plus peg-IFN α-2a/RBV for 28 days. **Co-intervention:** peg-IFN α-2a and RBV were administered according to the package insert for participants with genotype 1 infection. After end of treatment, participants continued treatment with peg-IFN α-2a/RBV alone for a further 44 weeks.
Outcomes	**Primary outcome:** AEs. **Secondary outcomes**: change in circulating HCV RNA at Week 4, percentage of participants with RVR at Week 4, percentage of participants with SVR at 12 and 24 weeks after last dose of peg+RBV following completion of 48 weeks of treatment, pharmacokinetics, percentage of participants who developed resistance to sofosbuvir.
Notes	We emailed Rodriguez-Torres and colleagues on 27 April 2016 for additional information on blinding during assessment, unpublished data, (mortality data) but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement

Rodriguez-Torres 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	The randomisation schedule was provided by PharStat, Inc. (NC, USA)
Allocation concealment (selection bias)	Low risk	Participants were randomised by a central web-based system using permutated blocks
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both investigators and participants were blinded to the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants dropped out during study
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT01054729) and all outcomes reported on
Vested-interest bias	High risk	This study was funded by Gilead Sciences, Inc.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2014a1

Methods	Randomised clinical trial
Participants	74 participants were randomised **Sex:** 49 men, 25 women **Mean age:** 54.3 years **Inclusion criteria:** participants 18-65 years of age with hepatitis C genotype 1 infection who had had unsuccessful prior treatment with standard P/R therapy and their screening HCV RNA level was 4 x 10^5 IU/mL or greater. Participants with cirrhosis by liver biopsy or noninvasive assessment (such as Fibroscan ultrasound and other approved methods according to the local standard of care) were enrolled in a separate cohort. The diagnosis of cirrhosis was based on the interpretation provided by the enrolling investigator. **Exclusion criteria:** complicated cirrhosis (defined per protocol as ascites, bleeding oesophageal varices, hepatic encephalopathy, or other signs or symptoms of decompensated cirrhosis), evidence of HCC, HIV co-infection, or any condition contraindicating re-treatment with P/R. Participants also were ineligible if recent laboratory tests showed hyperbilirubinaemia (total, > 2.4 mg/dL; or direct, > 1.0 mg/dL), hypoalbuminaemia (< 3.3 g/dL), anemia (< 13 g/dL for men or < 12 g/dL for women), thrombocytopenia (< 100 -103/mL), coagulopathy (international normalised ratio, > 1.2), or renal insufficiency (estimated creatinine clearance < 60 mL/min by the Cockcroft–Gault equation).
Interventions	**Experimental group:** 1. 600mg vaniprevir twice a day for 24 weeks with P/R for 24 weeks. 2. 600mg vaniprevir twice a day for 24 weeks with P/R for 48 weeks. 3. 600mg vaniprevir twice a day for 48 weeks with P/R for 48 weeks.

Rodriguez-Torres 2014a1 *(Continued)*

	4. 300mg vaniprevir twice a day for 48 weeks with P/R for 48 weeks. **Control group:** P/R plus placebo for 48 weeks. **Co-intervention:** P/R.
Outcomes	**Primary:** SVR rate, AEs, discontinuations due to AEs. **Secondary:** cEVR, SVR24 for 300 mg vaniprevir, and SVR24 for 600 mg vaniprevir 24 weeks.
Notes	We emailed Rodriguez-Torres and colleagues on 27 April 2016 for additional information on allocation concealment, randomisation, blinding of participants and personnel as well as outcome assessment, specification of il28b genotypes and the SVR rates for these. Missing data, number of participants analysed for HCV-related morbidity, sample size calculation, SAEs, but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded, but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants dropped out (5.4%) due to administrative discontinuations
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT00704405) and all outcomes reported on
Vested-interest bias	High risk	This study was sponsored and funded by Merck
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2014a2

Methods	For characteristics see Rodriguez-Torres 2014a1
Participants	
Interventions	
Outcomes	

Rodriguez-Torres 2014a2 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded, but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants dropped out (5.4%) due to administrative discontinuations
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT00704405) and all outcomes reported on
Vested-interest bias	High risk	This study was sponsored and funded by Merck
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2014a3

Methods	For characteristics see Rodriguez-Torres 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Rodriguez-Torres 2014a3 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded, but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants dropped out (5.4%) due to administrative discontinuations
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT00704405) and all outcomes reported on
Vested-interest bias	High risk	This study was sponsored and funded by Merck
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2014a4

Methods	For characteristics see Rodriguez-Torres 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was described as double-blinded, but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The studywas described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants dropped out (5.4%) due to administrative discontinuations

Rodriguez-Torres 2014a4 *(Continued)*

Selective reporting (reporting bias)	Low risk	A protocol was found (NCT00704405) and all outcomes reported on
Vested-interest bias	High risk	This study was sponsored and funded by Merck
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2014b1

Methods	Randomised clinical trial
Participants	288 participants were randomised. **Sex:** 153 men, 135 women **Mean age:** 47.8 years **Inclusion criteria:** treatment-naive (no prior treatment with IFN ± RBV or investigational anti-HCV agents). Male and female participants aged ≥ 18 years were eligible for inclusion in the study. All participants were required to be HCV seropositive, infected with a genotype 1 strain, and have plasma HCV RNA levels ≥ 10,000 IU/mL at screening. In addition, a non-cirrhotic fibrosis classification (i.e. Ishak score ≤ 4 or equivalent) from a liver biopsy obtained within 24 months of screening was required for enrolment. **Exclusion criteria:** co-infected with either HIV or hepatitis B, had evidence of severe or decompensated liver disease or liver disease unrelated to HCV infection, or had any pre-existing medical condition or laboratory abnormality that made them unsuitable for treatment with peg-IFN/RBV. Additional exclusion criteria included an abnormal ECG suggestive of clinically significant cardiac disease or QTc > 450 ms at screening, and history of solid organ transplant, or active alcohol or substance abuse sufficient to prevent adherence to study medication and/or follow-up. Lastly, female participants who were pregnant or nursing and male participants whose female partner was pregnant were excluded.
Interventions	**Experimental group:** 1. FLV dosed at 300 mg twice a day in combination with peg-IFN/RBV for 24 weeks 2. 600 mg twice a day in combination with peg-IFN/RBV for 24 weeks. **Control group:** placebo in combination with peg-IFN/RBV for 24 weeks peg-IFN (Pegasys) was administered at a dose of 180 µg subcutaneously once weekly. RBV (Copegus) was administered at 1000 mg twice a day for participants weighing ≤ 75 kg or 1200 mg twice a day for participants weighing > 75 kg. **Co-intervention:** peg-IFN/RBV.
Outcomes	**Primary:** proportion of participants who achieved SVR. **Secondary:** the proportion of participants with RVR, complete EVR, end of treatment response (ETR); the proportion of participants with relapsed viraemia; and patterns of AEs and safety measures.
Notes	We emailed Rodriguez-Torres and colleagues on 27 April 2016 for additional information on randomisation, allocation concealment, blinding of outcome assessment, unpublished data, overview of SAEs and the nature of the SAE but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement

Rodriguez-Torres 2014b1 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All sponsor personnel responsible for the conduct of the trial, with the exception of the sponsor study programmer, remained blinded to the results provided to the data monitoring committee. (Participants and investigators were unblinded to treatment assignment at week 24 to determine eligibility to discontinue therapy)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	67 participants dropped out
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT00987337) and the outcomes reported on
Vested-interest bias	High risk	This study was sponsored by Pfizer Inc.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2014b2

Methods	For characteristics see Rodriguez-Torres 2014b1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All sponsor personnel responsible for the conduct of the trial, with the exception of the sponsor study programmer, remained blinded to the results provided to the data monitoring committee. (Participants and investigators were unblinded to treatment assignment at week 24 to determine eligibility to discontinue therapy)

Rodriguez-Torres 2014b2 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	67 participants dropped out
Selective reporting (reporting bias)	Low risk	A protocol was found (NCT00987337) and the outcomes reported
Vested-interest bias	High risk	This study was sponsored by Pfizer Inc.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Rodriguez-Torres 2015

Methods	Randomised clinical trial
Participants	69 adult participants **Sex:** 49 men, 20 women **Mean age:** 50 years **Inclusion criteria:** chronic genotype 1-4 HCV infection, for cohorts 1-9, HCV RNA ≥ 100,000 IU/mL at screening (no HCV RNA restriction for cohort 10), screening laboratory values within defined thresholds and use of 2 effective contraception methods if female of childbearing potential or sexually active male **Exclusion criteria:** pregnant or nursing woman or man with pregnant female partner, presence of cirrhosis, prior exposure to approved or experimental HCV protease inhibitors, co-infection with HIV or HBV, current or prior history of clinical hepatic decompensation, chronic use of systemic immunosuppressive agents, history of clinically significant illness or any other medical disorder that may interfere with participant treatment, assessment or compliance with the protocol.
Interventions	**Experimental group:** 1: GS-9857 up to 300 mg (genotype 1a) for 3 days. 2: GS-9857 up to 300 mg (genotype 3) for 3 days. 3: GS-9857 up to 300 mg (genotype 2) for 3 days. 4-9: GS-9857 up to 600 mg (genotype 1a, 1b, 2, 3, or 4) for 3 days. 10: GS-9857 100 mg on Day 1 and GS-9857 100 mg plus SOF/GS-5816 on Days 2 and 3. **Control group:** placebo.
Outcomes	Safety, antiviral activity.
Notes	We contacted the trial authors about allocation sequence generation and concealment, how blinding was maintained, if outcome assessors were blinded, how many participants dropped out, SAE, death, SVR.
Risk of bias	

Rodriguez-Torres 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described that the control group received placebo but the similarity of the placebo with the study drug was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants dropped out
Selective reporting (reporting bias)	Unclear risk	No prepublished protocol could be found (NCT02185794 was published after the start of the trial)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Gilead Sciences)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Sarrazin 2007

Methods	Randomised clinical trial
Participants	26 adult participants **Inclusion criteria:** participants who could be of either sex and any race could be included in this study if they were 18-60 years of age, were willing to give written informed consent, and were willing to undergo multiple inpatient periods and outpatient visits during the study. Female participants had to be surgically sterile or of non-childbearing potential, and men had to practice acceptable methods of contraception. Female partners of male enrollees also had to practice acceptable methods of contraception, and all contraception had to have been practiced for 30 days before the dosing period during all dosing periods, and for 30 days after discontinuation of dosing. Participants had to be serum positive for HCV RNA by quantitative polymerase chain reaction assay, with 100,000 IU/mL RNA and be genotype 1a or 1b nonresponders to peg-IFN-2b with or without RBV. Nonresponse was defined as achieving < a 2-log10 decline in HCV RNA levels after at least 12 weeks of dosing with peg-IFN-2b at 1.5 g/kg/week. Participants had to have ALT and AST 5 times ULN, -fetoprotein values within normal levels, negative screen for drugs with high potential for abuse, normal or clinically acceptable ECG (QTc value, 450 milliseconds (ms) for women and 430 ms for men), and evidence of compensated liver disease. Participants were required to meet the following criteria: haemoglobin 11 g/dL for women and 12 g/dL for men, white blood cells 4000/mm3, neutrophil count 1500/mm3, and platelets 100,000/mm3 and the following parameters within normal limits: direct bilirubin, indirect bilirubin, albumin, prothrombin time, activated partial thromboplastin time, and serum creatinine. **Exclusion criteria:** participants were excluded from the study if they met any of the following criteria: haemophilia or use of anticoagulant therapy; evidence of advanced liver disease (e.g. known cirrhosis, history or presence of ascites, bleeding varices, encephalopathy); presence of organ transplant; known

Sarrazin 2007 *(Continued)*

	HIV or HBV positivity based on recent tests for anti-HIV antibodies and hepatitis B surface antigen; or liver disease with a cause other than chronic hepatitis C. The significance of antinuclear antibodies, if present, was to be evaluated by investigators for individual participants to determine whether any interference with the protocol that would warrant exclusion from the study could be expected.
Interventions	**Experimental group:** 1. SCH 503034 monotherapy for 1 week of either 200 mg or 400 mg three times a day. 2. administration of combination SCH 503034 plus peg-IFN-2b for 2 weeks. The SCH 503034 could be 200 mg or 400 mg three times a day. **Control group:** peg-IFN-2b monotherapy administered at 1.5 g/kg once per week.
Outcomes	Antiviral activity, safety, pharmacokinetics.
Notes	We emailed Sarrazin and colleagues on 27 April 2016 for additional information on prepublished protocol, data on SAE, death, SVR24 before the second phase began, allocation concealment but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was described as an open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial was described as an open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants completed the first phase of the trial
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was conducted at the Schering-Plough Research Institute
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Schiff 2008

Methods	Randomised clinical trial
Participants	357 participants

Schiff 2008 *(Continued)*

	Inclusion criteria: prior null responders with chronic hepatitis C genotype 1, with no evidence of cirrhosis on liver biopsy, results of physical examination and laboratory tests within specified ranges and abstinence from use of abused substances. **Exclusion criteria:** women who were pregnant or nursing a child, participants with cirrhosis, co-infection with Hepatitis B or HIV, and African-American participants, previous treatment with any HCV polymerase or protease inhibitor, participants who relapsed following response to previous treatment, evidence of advanced liver disease, or liver disease from a cause other than chronic hepatitis C, pre-existing psychiatric condition.
Interventions	**Experimental group:** 2: boceprevir 100 mg orally three times a day for 48 weeks. 3: boceprevir 200 mg orally three times a day for 48 weeks. 4: boceprevir 400 mg orally three times a day for 24 weeks 5: boceprevir 400 mg orally three times a day + RBV. 6: boceprevir 400 mg orally three times a day for 48 weeks. 7: boceprevir 800 mg orally three times a day. 8 (added as an amendment): boceprevir 800 mg + RBV. **Control group:** (arm 1): placebo + a single dose of peg was given first, followed 1 week later by peg + RBV for 12 weeks. If participant was HCV RNA negative, peg + RBV was continued for another 36 weeks. **Co-intervention:** peg-IFN alfa-2b (1.5 mg/kg/wk).
Outcomes	Pharmacokinetics, antiviral activity, safety.
Notes	Control group crossed over at week 17 if with detectable HCV RNA at week 12. Data needed to be available prior to week 12 before we could report the data. We contacted the trial authors on 06 June 2016 for additional information on allocation sequence generation and concealment, maximum follow-up, how many participants dropped out, how was missing data handled, was there a prepublished protocol other than ClinicalTrials.gov, SAE, death, SVR24, data at week 12, and how much RBV was given but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded but the placebo was not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	There was above 5% dropouts and it was unclear how the trial handled missing data

Schiff 2008 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Secondary outcomes were first added after the trial was completed
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Merck Sharp and Dohme Corp.)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Silva 2013a1

Methods	Randomised clinical trial
Participants	39 participants were randomised to treatment **Sex:** 32 men, 7 women **Mean age:** 41.5 years **Inclusion criteria:** male and female participants aged 18–60 years, with a BMI between 18 and 29 kg/m2 were enrolled. All participants were serum positive for HCV RNA by quantitative PCR assay, classified as G2/3, and naive to treatment for HCV infection. They were required to have ALT and AST 65 times ULN, no evidence of HCC (per ultrasound and serum alfa-fetoprotein levels), and haematologic and biochemical evidence of compensated liver disease. **Exclusion criteria:** participants with a history of substance abuse within 1 year of study participation, or any clinically significant medical disorder, such as HIV or HBV infection, haemophilia, or evidence of other liver disease not caused by chronic hepatitis C were excluded.
Interventions	**Experimental group** 1. boceprevir 200 mg twice a day or placebo. 2. boceprevir 400 mg twice a day or placebo. 3. boceprevir 400 mg three times a day or placebo for 14 days. **Control group:** placebo. **Co-intervention:** none.
Outcomes	**Primary:** to evaluate the safety and tolerability of boceprevir. **Secondary:** pharmacokinetics and changes in HCV RNA viral load.
Notes	We emailed Silva and colleagues on 27 April 2016 for additional information on allocation concealment, unpublished data, SVR data, (AEs and non serious AEs listed) plus published protocols but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code provided by the sponsor (Schering-Plough Research Institute)

Silva 2013a1 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as double-blinded, (active drug and matched placebo capsules were used to maintain third-party blind dispensing)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant dropped out due to AE
Selective reporting (reporting bias)	Unclear risk	Protocol not found
Vested-interest bias	High risk	This study was supported by Merck & Co. Inc.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Silva 2013a2

Methods	For characteristics see Silva 2013a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random code provided by the sponsor (Schering-Plough Research Institute)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as double-blinded, (active drug and matched placebo capsules were used to maintain third-party blind dispensing)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.

Silva 2013a2 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant dropped out due to AE
Selective reporting (reporting bias)	Unclear risk	Protocol not found
Vested-interest bias	High risk	This study was supported by Merck & Co., Inc.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Silva 2013a3

Methods	For characteristics see Silva 2013a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated random code provided by the sponsor (Schering-Plough Research Institute)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described as double-blinded, (Active drug and matched placebo cap-sules were used to maintain third-party blind dispensing)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blinded but it was unclear how the blinding was maintained and who performed the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant dropped out due to AE
Selective reporting (reporting bias)	Unclear risk	Protocol not found
Vested-interest bias	High risk	This study was supported by Merck & Co. Inc.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Sims 2014

Methods	Randomised clinical trial
Participants	24 participants **Sex:** 18 men, 6 women **Mean age:** 45.8 years **Country:** USA **Inclusion criteria:** men and women aged 18-60 years with chronic HCV genotype 1 infection, a screening plasma HCV RNA level of at least 100,000 IU/mL, and a BMI between 18 and 35 kg/m2. Participants were noncirrhotic (screening FibroTest score of 0.59 with an aminotransferase/platelet ratio index of 2 or with absence of cirrhosis documented by biopsy within the previous 12 months) and could be either treatment-naive or have previously received and discontinued alfa IFN, with or without RBV, at least 6 months before enrolment. **Exclusion criteria:** previous exposure to HCV NS5A or NS5B inhibitors, co-infected with HIV or HBV or infected with other HCV genotypes. Pregnant or nursing women were also excluded, as were women of childbearing age unwilling to use contraception from 1 month predose through 8 weeks postdose. Men were excluded if unwilling to practice barrier contraception with female partners for at least 12 weeks postdose.
Interventions	The trial was divided into 4 different cohorts comprising **Experimental group:** oral 100 mg, 300 mg, 600 mg, and 900 mg of BMS-791325 for 5 days. **Control group:** placebo.
Outcomes	Safety assessment, HCV RNA assessment, pharmacokinetics
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated scheme
Allocation concealment (selection bias)	Low risk	Interactive voice-response telephone system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded, but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded, but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

Sims 2014 *(Continued)*

Selective reporting (reporting bias)	High risk	The trial added extra primary outcomes in ClinicalTrials.gov (NCT00664625)
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

STARTVerso-1 2015a1

Methods	Randomised multicenter phase III clinical trial
Participants	656 participants **Sex:** 342 men, 314 women **Mean age:** 47.6 years **Countries:** 10 European countries and Japan **Inclusion criteria:** treatment-naïve, aged 18–70 years (Europe), or 20–70 years (Japan), with chronic HCV genotype 1 infection diagnosed by positive anti-HCV antibodies and HCV RNA > 1000 IU/mL at screening plus a positive antibody or HCV RNA test more than 6 months before screening, or a liver biopsy consistent with chronic HCV infection. Participants with compensated liver disease, including cirrhosis, were eligible for inclusion. All participants had a liver biopsy within 3 years or had a FibroScan within 6 months of randomisation to determine fibrosis stage. For participants without a liver biopsy, fibrosis stage was determined by FibroScan results using a cut-off value of 9.5 kPa to indicate fibrosis stage > F3 (< 9.5 kPa F0–F2; > 9.5 kPa F3–F4), consistent with evaluations of the use of FibroScan in chronic HCV however, there are no reliable cut-offs in the literature for distinguishing < F3 from > F3. The FibroScan threshold for cirrhosis was > 13 kPa. **Exclusion criteria:** HCV infection of mixed genotype (1/2, 1/3, and 1/4) diagnosed by genotypic testing at screening, evidence of acute or chronic liver disease due to causes other than chronic HCV infection, HIV co-infection, HBV infection based on presence of HBs-Ag, active malignancy, or history of malignancy within the last 5 years prior to screening (with an exception of appropriately treated basal cell carcinoma of the skin or in situ carcinoma of the uterine cervix), active or, history of alcohol or illicit drug abuse other than cannabis within the past 12 months, a condition that is defined as one which in the opinion of investigator may put the patient at risk because of participation in this study, may influence the results of this study, or limit the patient's ability to participate in this study, usage of any investigational drugs within 28 days prior to screening, or planned usage of an investigational drug during the course of this study, received concomitant systemic antiviral, hematopoietic growth factor, or immunomodulatory treatment within 28 days prior to screening. Participants being treated with oral antivirals such as acyclovir, famciclovir or valacyclovir for recurrent herpes simplex infection; or with oseltamivir or zanamivir for influenza A infection, may be screened, received silymarin (milk thistle), glycyrrhizin, or Sho-saiko-to (SST) within 28 days prior to screening and throughout the treatment phase, known hypersensitivity to any ingredient of the study drugs, alpha fetoprotein value > 100 ng/mL at screening; if > 20 ng/mL and = 100 ng/mL, participants may be included if there is no evidence of liver cancer in an appropriate imaging study (e.g. ultrasound, CT scan, or MRI) within last 6 months prior to randomisation (Visit 2), decompensated liver disease, or history of decompensated liver disease, as defined by the presence of: hepatic encephalopathy, ascites, or oesophageal variceal bleeding and/or laboratory results of any of the following: international normalized ratio = 1.7; serum albumin = 3.5 g/dL; serum total bilirubin = 2.0 mg/dL (except when the increase is predominately due to unconjugated bilirubin and related to Gilbert's syndrome), pre-existing psychiatric condition that could interfere with the participant's participation in and completion of the study including but not limited to prior suicidal attempt, schizophrenia, major depression syndrome, severe anxiety, severe personality disorder, a period of disability or impairment due to a psychiatric disease within the past 5 years.

STARTVerso-1 2015a1 *(Continued)*

Interventions	**Experimental group 1:** faldaprevir 120 mg once daily. Those with early treatment success (ETS, HCV RNA < 25 IU/mL target detected() or target not detected() at week 4 and < 25 IU/mL TND at week 8) stopped faldaprevir at week 12 and received placebo plus peg-IFN and RBV for a further 12 weeks. Participants without ETS received faldaprevir plus peg-IFN and RBV for 24 weeks. **Experimental group 2**: faldaprevir 240 mg once daily plus peg-IFN and RBV for 12 weeks followed by placebo plus peg-IFN and RBV to week 24, and either stopped treatment (early treatment success) or continued peg-IFN and RBV to week 48 (no early treatment success). **Control group:** placebo. **Co-intervention:** all participants received peg-IFNα-2a administered subcutaneously at 180 lg once weekly. RBV administered orally at a total dose of 1000 or 1200 mg (for bodyweight < 75 kg or P75 kg, respectively) daily in 2 divided doses, except in Japan where the total dose was 600, 800, or 1200 mg (for bodyweight 660 kg, > 60–680 kg, or > 80 kg, respectively) daily in 2 divided doses according to the local label peg-IFN and RBV for 24 weeks after intervention period. All study medication was stopped in the event of virologic breakthrough at or after week 4 (increase in HCV RNA > 1 log10 from nadir or > 25 IU/mL after an initial decrease to < 25 IU/mL), lack of EVR (decrease in HCV RNA P2 log10 from baseline at week 12), or lack of virologic response (detectable HCV RNA at week 24).
Outcomes	Safety assessment, SVR, AST or ALT normalisation, early treatment success.
Notes	We contacted the trial authors for additional information on sequence generation, blinding, who was blinded for the HCV RNA results, missing data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	The trial used interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators, sponsor, and participants were blinded to treatment group allocation through the use of matching placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	High risk	HCV RNA results were only blinded up to week 8
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out (and 34% dropped out of the placebo-group) and it was unclear if the trial used proper methodology to account for this
Selective reporting (reporting bias)	High risk	The trial changed the primary outcomes from the original version
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim Pharmaceuticals, GmbH & Co. KG
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

STARTVerso-1 2015a2

Methods	For characteristics see STARTVerso-1 2015a2
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	The trial used interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators, sponsor, and participants were blinded to treatment group allocation through the use of matching placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	High risk	HCV RNA results were only blinded up to week 8
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out (and 34% dropped out of the placebo-group) and it was unclear if the trial used proper methodology to account for this
Selective reporting (reporting bias)	High risk	The trial changed the primary outcomes from the original version
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim Pharmaceuticals, GmbH & Co. KG.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

STARTverso-2 2014a1

Methods	Randomised multicenter phase III clinical trial (STARTverso-2)
Participants	658 participants **Sex:** 389 men, 268 women **Mean age:** 50.3 **Inclusion criteria:** treatment-naive, 18–70 years (Europe), or 20–70 years (Japan), with chronic HCV genotype 1 infection diagnosed by positive anti-HCV antibodies and HCV RNA > 1000 IU/ml at screening plus a positive antibody or HCV RNA test more than 6 months before screening, or a liver biopsy consis-

STARTverso-2 2014a1 *(Continued)*

	tent with chronic HCV infection. Patients with compensated liver disease, including cirrhosis, were eligible for inclusion. All participants had a liver biopsy within 3 years or had a FibroScan within 6 months of randomisation to determine fibrosis stage. For participants without a liver biopsy, fibrosis stage was determined by FibroScan results using a cut-off value of 9.5 kPa to indicate fibrosis stage > F3 (< 9.5 kPa F0–F2; > 9.5 kPa F3–F4), consistent with evaluations of the use of FibroScan in chronic HCV however, there are no reliable cut-offs in the literature for distinguishing < F3 from > F3. The FibroScan threshold for cirrhosis was > 13 kPa. **Exclusion criteria:** mixed genotype HCV; HIV or hepatitis B co-infection; decompensated liver disease; and contraindications to peg-IFN or RBV. Asian participants were limited to 20% of the total population.
Interventions	**Experimental group 1:** faldaprevir (BI 201335) 120 mg once daily (oral), for 24 weeks, with pegylated IFN α-2a (peg-IFN/RBV), subcutaneous injection/oral. At week 24, if the participants did not achieve early treatment success they received an additional 24 weeks of peg-IFN/RBV alone. **Experimental group 2:** faldaprevir 240 mg once daily. faldaprevir 240 mg once daily (oral), for 12 weeks, with peg-IFN/RBV (subcutaneous injection/oral). Followed by an additional 12 weeks of placebo plus peg-IFN/RBV. At week 24, if the participants did not achieve early treatment success they received an additional 24 weeks of peg-IFN/RBV alone. **Control group:** placebo (oral) once daily combined with peg-IFN/RBV (subcutaneous injection) for 24 weeks, followed by an additional 24 weeks of peg-IFN/RBV (oral) alone.
Outcomes	Safety assessment, SVR, AST or ALT normalisation, early treatment success.
Notes	Email was sent to Asselah and colleagues on 20 April 2016 for additional information on primary publication, randomisation, blinding, all bias, death but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded but the placebo was not further described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out and the trial did not report how they dealt with missing data
Selective reporting (reporting bias)	High risk	The trial changed the primary outcomes from the original version
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

STARTverso-2 2014a2

Methods	For characteristics see STARTverso-2 2014a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blinded but the placebo was not further described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out and the trial did not report how they dealt with missing data
Selective reporting (reporting bias)	High risk	The trial changed the primary outcomes from the original version
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

STARTverso-3 2013a1

Methods	Randomised clinical trial
Participants	678 participants **Sex:** 403 men, 274 women **Mean age:** 53.4 years **Inclusion criteria:** chronic hepatitis C genotype 1 infection, diagnosed at least 6 months prior to screening, confirmed prior virological failure with an approved dose of peg-IFN/RBV age 18-70 years, HCV RNA = 1000 IU/mL at screening.

STARTverso-3 2013a1 *(Continued)*

	Exclusion criteria: HCV infection of mixed genotype; HBV or HIV co-infection. Evidence of acute or chronic liver disease due to causes other than chronic HCV infection, decompensated liver disease, or history of decompensated liver disease. Body weight < 40 or > 125 kg, clinical evidence of significant or unstable cardiovascular disease, chronic pulmonary disease, history or evidence of retinopathy or clinically significant ophthalmological disorder. Pre-existing psychiatric condition that could interfere with the participant's participation in and completion of the study, laboratory parameters disorders (thalassaemia major, sickle cell anaemia or G6PD deficit). Haemoglobin < 12 g/dL for women and < 13 g/dL for men, participants who had been previously treated with at least 1 dose of any antiviral or immunomodulatory drug other than IFN alfa or RBV for acute or chronic HCV infection including and not restricted to protease or polymerase inhibitors.
Interventions	The trial was divided into 3 cohorts according to virological failure (relapse, partial, null response) and randomised to 1 of the following groups: **Experimental group 1:** participants received faldaprevir 240 mg once daily, in the form of 2 soft gelatin capsules administered orally, combined with peg-IFN/RBV, administered by injection, for 12 weeks, followed by placebo once daily combined with peg-IFN/RBV for 12 weeks **Experimental group 2:** participants received faldaprevir 240mg once daily, in the form of 2 soft gelatin capsules administered orally, combined with peg-IFN/RBV, administered by injection, for 24 weeks. **Control group:** received 2 soft gelatin capsules identical to those containing faldaprevir once daily (orally) and peg-IFN α-2a/RBV) administered by injection, for 24 weeks. **Co-intervention:** At week 24, if the participants did not achieve early treatment success the participants received an additional 24 weeks of peg-IFN/RBV alone.
Outcomes	SVR, early treatment success, AST, ALT normalisation, safety.
Notes	We emailed Jacobson and colleagues on 26 April 2016 for additional information on primary publication, randomisation, blinding, all bias, death but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being blinded but method was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being blinded but method was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out and the trial did not report how they dealt with missing data
Selective reporting (reporting bias)	High risk	The trial changed the primary outcomes from the original version (NCT01358864)
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim

STARTverso-3 2013a1 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

STARTverso-3 2013a2

Methods	For characteristics see STARTverso-3 2013a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being blinded but method was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being blinded but method was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out and the trial did not report how they dealt with missing data
Selective reporting (reporting bias)	High risk	The trial changed the primary outcomes from the original version (NCT01358864)
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

STARTverso-3 2013a3

Methods	For characteristics see ADVANCE 2011a2
Participants	

STARTverso-3 2013a3 *(Continued)*

Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being blinded but method was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being blinded but method was not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out and the trial did not report how they dealt with missing data
Selective reporting (reporting bias)	High risk	The trial changed the primary outcomes from the original version (NCT01358864)
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

STARTverso-4 2015

Methods	Randomised clinical trial
Participants	308 participants **Sex:** 248 men, 60 women **Mean age:** 46.9 years **Inclusion criteria:** 18–70 years, had chronic HCV genotype 1 infection (positive anti-HCV antibody and HCV RNA > 1000 IU/mL at screening, and documented positive anti-HCV antibody or HCV RNA > 1000 IU/ mL > 6 months prior to screening), and chronic HIV infection (HIV-1 viral load testing or HIV-1 western blot at screening and documented for > 6 months prior to screening) with a Karnofsky score greater than 70. HCV treatment-naive individuals and those with prior relapse after completion of an IFN-based regimen (detectable HCV/RNA < 24weeks after treatment with undetectable HCV/RNA at end of treatment) were eligible. Individuals naive to highly active antiretroviral therapy (HAART) were required to have a CD4þ cell count at least 500 cells/mL and HIV plasma RNA below 100,000 copies/mL at screening; those stabilised on HAART (HIV-1 plasma RNA < 40 copies/mL at screening and < 50 copies/mL for > 6 months before randomisation) were required to have been on an acceptable combination of anti-

STARTverso-4 2015 *(Continued)*

	retrovirals (as defined in the protocol, Supplemental Table S1, http://links.lww.com/QAD/A638) for at least 6 weeks prior to randomisation and to have a CD4þ cell count at least 200 cells/mL. Individuals prescribed an atazanavir/ritonavir-containing HAART regimen were required to have total bilirubin 2.5 times or less the ULN at screening. Documentation of a liver biopsy < 3 years or liver elastography < 6 months of randomisation was mandatory. **Exclusion criteria:** mixed genotype HCV, evidence of non-HCV-related liver disease, hepatitis B infection, decompensated liver disease, and hypersensitivity to the study treatments.
Interventions	**Experimental group:** faldaprevir 240 mg for additional 12 weeks **Control group:** no intervention **Co-intervention:** peg-IFN and RBV + faldaprevir 240 mg for the first 12 weeks
Outcomes	ALT, AST, SVR, SAE, mortality.
Notes	Only the group with faldaprevir 240 mg 12W and faldaprevir 240 mg 24W could be used for analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice-response system
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants from the experimental group dropped out, while none from the control group dropped out
Selective reporting (reporting bias)	Low risk	A protocol were published and the trial reported all outcomes (NCT01399619)
Vested-interest bias	High risk	The trial was funded by Boehringer Ingelheim Pharma GmbH & Co. KG.
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Sulkowski 2013a

Methods	Randomised clinical trial
Participants	62 participants **Sex:** 53 men, 7 women (60 analysed)

Sulkowski 2013a *(Continued)*

	Mean age: 44.5 years (60 analysed) **Countries:** France, Germany, Spain and USA. **Inclusion criteria:** treatment-naive participants age of 18-65 years, genotype 1 chronic HCV infection, chronic HIV-1 infection, no previous HCV treatment, and haemoglobin levels of 120 g/L or greater in women and 130 g/L or greater in men. Participants were required to have stable HIV disease defined as follows: part A (no antiretroviral therapy) participants had CD4 counts of ≥ 0.500 x 10^ cells/L and HIV RNA levels of ≤ 100,000 copies/mL, and part B (antiretroviral therapy for > 12 weeks) participants had CD4 counts of ≥ 0.300 x 10^ cells/L and HIV RNA levels < 50 copies/ mL. For part B, permissible antiretroviral regimens were efavirenz, tenofovir, and emtricitabine, or ritonavir-boosted atazanavir, tenofovir, and either emtricitabine or lamivudine. **Exclusion criteria:** hepatic decompensation; other causes of significant liver disease, cancer within 5 years, significant cardiac dysrhythmia, and active AIDS-related conditions within 6 months. All participants had liver biopsies within 1 year unless previous biopsies indicated cirrhosis; histologic assessment according to the METAVIR scoring system was done by a local pathologist.
Interventions	**Experimental group:** oral 750 mg of telaprevir 3 times daily for 12 weeks (when the antiretroviral therapy included efavirenz, telaprevir dosage was 1125 3 times daily for 8 weeks). **Control group:** placebo. **Co-intervention:** peg-IFN 2a (180 µg/wk) and RBV (800 mg/d) for a total of 48 weeks.
Outcomes	Safety assessment, efficacy assessment, SVR, pharmacokinetics.
Notes	NCT00983853 participants were randomised in cohorts according to HIV-treatment. We emailed Sulkowski and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	The trial used interactive web-response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was only blinded for the first 24 weeks
Blinding of outcome assessment (detection bias) All outcomes	High risk	The trial was only blinded for the first 24 weeks
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	High risk	The trial changed the primary outcome. Safety assessments were originally a primary outcome, this was changed
Vested-interest bias	High risk	The trial was funded by Vertex pharmaceuticals

Sulkowski 2013a *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Sulkowski 2013b

Methods	Randomised clinical trial
Participants	99 participants **Sex:** 68 men, 31 women **Mean age:** 44 years **Countries:** Argentina, Belgium, Canada, France and USA. **Inclusion criteria:** aged 18–65 years who were infected with both HIV and HCV at 30 academic and non-academic study sites. Eligible participants had to have untreated, chronic HCV genotype 1 infection without hepatic decompensation, plasma HCV RNA of more than 10,000 IU/mL at screening, no infection with other HCV genotypes, and a liver biopsy sample with histological findings consistent for chronic hepatitis C (and no other cause), participants with a history of HIV infection for > 6 months and stable HIV disease, with a CD4 cell count of ≥ 200 cells per µL and HIV-1 RNA viral load of < 50 copies per mL. **Exclusion criteria:** HBV surface antigen positive; use of didanosine, zidovudine, efavirenz, or other non-nucleoside reverse transcriptase inhibitors; a neutrophil count of < 1500 cells per µL; a haemoglobin concentration of < 110 g/L for women and < 120 g/L for men; or a platelet count of < 100,000 platelets per µL.
Interventions	**Experimental group:** 800 mg of boceprevir (MK-3034) twice a day for 44 weeks. **Control group:** placebo. **Co-intervention:** peg-IFN–RBV for 4 weeks prior to intervention period. Additional 44 weeks of Peg-IFN alfa-2b 1.5 µg/kg administered once weekly by subcutaneous injection. RBV 600 mg–1400 mg per day (weight-based) was taken orally twice daily with food. Erythropoietin was permitted if haemoglobin concentrations decreased to < 100 g/L.
Outcomes	Pharmacokinetics, safety assessment, laboratory values.
Notes	After 12 weeks of treatment the control group was allowed to cross-over to the experimental group, therefore no data could be used. (NCT01482767) We emailed Sulkowski and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Interactive voice-response system
Blinding of participants and personnel (performance bias)	High risk	All study site personnel (including the investigators), the sponsor, and participants were masked to treatment assignment until final database lock. But it

Sulkowski 2013b *(Continued)*

All outcomes		was unclear when final database lock was defined. Additionally control group were allowed to crossover.
Blinding of outcome assessment (detection bias) All outcomes	High risk	All study site personnel (including the investigators), the sponsor, and participants were masked to treatment assignment until final database lock. But it was unclear when final database lock was defined. Additionally control group were allowed to crossover
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	The trial was funded by Merck
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Sulkowski 2013c

Methods	A phase IIb, multicenter, randomised, double-blind, placebo-controlled, parallel-group trial (SILEN-C1) (NCT00774397)
Participants	429 participants **Sex:** 234 men, 195 women **Mean age ± SD:** 46 ± 10.5 years **Country:** Argentina, Australia, Austria, Canada, Czech Republic, France, Germany, Republic of Korea, the Netherlands, Portugal, Romania, Spain, Switzerland, UK, and USA. **Inclusion criteria:** age between 18 and 65 years, chronic hepatitis C infection genotype 1, treatment-naive, HCV RNA > 100,000 IU/mL. A liver biopsy within 24 months before enrolment providing histologic evidence of any degree of chronic necroinflammatory activity or the presence of fibrosis, but no evidence of cirrhosis, a normal retinal finding on fundoscopy within 6 months before enrolment. **Exclusion criteria:** HCV of mixed genotype, HBV or HIV co-infection, decompensated liver disease, hyperbilirubinaemia > 1.5 ULN, concomitant treatment with medications that are substrates of P-gp, UGT1A1, CYP3A4 or 2C9. **Group 1:** 71 participants Sex: 41 men, 30 women Mean age ± SD: 46 ± 10.9 years Ethnicity, n(%): Asian: 8(11), black: 4(6), white: 57(80), other: 2(3) HCV genotype, n(%): 1: 1(1), 1a: 32(45), 1b: 38(54). 3a, 4a, 6e, 6q: 0 IL28B genotype, n(%): CC: 11(15), non-CC: 29(41), missing: 31(44) **Group 2:** 69 participants Sex: 40 men, 29 women Mean age ± SD: 46 ± 10.9 years

Sulkowski 2013c *(Continued)*

	Ethnicity, n(%): Asian: 9(13), black: 1(1), white: 58(84), other: 1(1) HCV genotype, n(%): 1: 0, 1a: 19(28), 1b: 50(72). 3a, 4a, 6e, 6q: 0 IL28B genotype, n(%): CC: 8(12), non-CC: 33(48), missing: 28(41) **Group 3:** 143 participants Sex: 74 men, 69 women Mean age ± SD: 45 ± 10.2 years Ethnicity, n(%): Asian: 21(15), black: 1(1), white: 119(83), other: 2(1) HCV genotype, n(%): 1: 0, 1a: 67(47), 1b: 74(52). 3a, 4a, 6e, 6q: 2(1) IL28B genotype, n(%): CC: 19(13), non-CC: 53(37), missing: 71(50) **Group 4:** 146 participants Sex: 79 men, 67 women Mean age ± SD: 46 ± 10.5 years Ethnicity, n(%): Asian: 17(12), black: 4(3), white: 122(84), other: 3(2) HCV genotype, n(%): 1: 0, 1a: 51(35), 1b: 91(62). 3a, 4a, 6e, 6q: 4(3) IL28B genotype, n(%): CC: 22(15), non-CC: 48(33), missing: 76(52).
Interventions	**Experimental group:** 2: faldaprevir 120 mg once daily for 24 weeks, 3: faldaprevir 240 mg once daily for 24 weeks, 4: faldaprevir 240 mg once daily for 24 weeks. **Control group:** 1: placebo once daily for 24 weeks. **Co-interventions:** 2 and 3: peg-IFN alfa-2a 180 µg once weekly and oral weight-based RBV 1000 mg-1200 mg daily in 2 divided doses for 48 weeks with a 3-day lead in period given with placebo. 1 and 4: peg-IFN alfa-2a 180 µg once weekly and oral weight-based RBV 1000 mg to 1200 mg daily in 2 divided doses for 48 weeks.
Outcomes	**Primary outcome:** sustained virological response 24 weeks after end of treatment **Secondary outcomes:** number of participants with virological rebound (HCV RNA < 1 $\log_{10}$ from nadir, or ≥ 100 IU/mL after previous viral load below the lower limit of detection in 2 consecutive visits at least 2 weeks apart. Number of participants with breakthrough (HCV RNA rebound during treatment). Number of participants with relapse (HCV RNA undetectable at end of treatment, but detectable during the follow-up period). Number of participants with no response (participants who did not achieve SVR, but did not experience a virological breakthrough or relapse).
Notes	We emailed Sulkowski and colleagues on 27 April 2016 for additional information on random sequence generation, allocation concealment, description of blinding, blinding of outcome assessors but reply not received yet.

Risk of bias

Sulkowski 2013c *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors stated that participants and investigators were blinded to treatment groups until 24 weeks after the end of treatment, but the method of blinding was not sufficiently described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not mentioned if outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for treatment discontinuation and withdrawal were clearly stated. From 23%-40% in the 3 groups of participants discontinued treatment, mostly due to lack of efficacy
Selective reporting (reporting bias)	Low risk	A protocol was published before randomisation began and all outcome results were reported adequately
Vested-interest bias	Unclear risk	The study was sponsored by Boehringer Ingelheim
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias

Sullivan 2012

Methods	Randomised clinical trial
Participants	37 adult participants **Sex:** 22 men, 15 women **Mean age:** 48.3 years **Inclusion criteria:** chronic hepatitis C genotype 1, who were treatment-naive participants, where women had to be either postmenopausal for at least 2 years or surgically sterile and men had to be surgically sterile or practicing specific forms of birth control and had documented FibroTest score in combination with an AST to Platelet Ratio Index, or a liver biopsy within the last 12 months to document absence of cirrhosis. **Exclusion criteria:** pregnant or breastfeeding woman, use of any medications contraindicated for use with peg-IFN or RBV 2 weeks prior to study drug administration or 10 half-lives, whichever was longer, clinically significant cardiac, respiratory (except mild asthma), renal, gastrointestinal, haematologic, neurologic disease, or any uncontrolled medical illness or psychiatric disease or disorder, current or past clinical evidence of cirrhosis or bridging fibrosis, abnormal screening laboratory results.
Interventions	**Experimental group:** 1. 5 mg once a day. 2. 50 mg once a day. 3. 2000 mg once a day.

Sullivan 2012 *(Continued)*

	Control group: placebo **Co-intervention:** peg-IFN α-2a 180 µg/week + weight-based RBV 1000 mg-1200 mg/day for 48 weeks.
Outcomes	
Notes	We emailed Sullivan and colleagues on 27 April 2016 for additional information on allocation sequence generation and concealment, description of placebo, and prepublished protocol but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded (participant, caregiver, investigator, outcomes assessor) but it was unclear how well matched the placebo was
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as double-blinded (participant, caregiver, investigator, outcomes assessor) but it was unclear how well matched the placebo was
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how the trial handled missing data (many were lost to follow-up but still 'included' in the analyses)
Selective reporting (reporting bias)	High risk	The primary and secondary outcomes were changed after the trial was completed (NCT01314261)
Vested-interest bias	Unclear risk	The trial was funded by a company that might have an interest in a given result (AbbVie)
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Tanwandee 2012

Methods	Randomised clinical phase II trial
Participants	24 adults with chronic hepatitis C, genotype 1, who were naive to antiviral treatment. **Country:** Thailand **Exclusion criteria:** not described.
Interventions	**Experimental group:** oral 200 mg, 400 mg of BIT225 for 28 days. **Control group:** placebo. **Co-intervention:** IFN alfa 2b and RBV for a total of 48 weeks.

Tanwandee 2012 *(Continued)*

Outcomes	SVR, safety, pharmacokinetics.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being placebo-blinded, but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being placebo-blinded, but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data
Selective reporting (reporting bias)	Unclear risk	No protocol could be obtained
Vested-interest bias	High risk	The trial was funded by Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Tatum 2015a1

Methods	Randomised phase II clinical trial
Participants	39 participants **Country:** USA **Inclusion criteria:** treatment-naive adults chronically infected with HCV genotype 1 adult participants. Participants were required to have HCV RNA ≥ 10–5 IU/mL (COBAS TaqMan HCV Test 2.0; Roche Molecular Diagnostics, Pleasanton, California; lower limit of quantitation (LLOQ) 25 IU/mL) at screening, with no evidence of cirrhosis by liver biopsy within 24 months of randomisation. **Exclusion criteria:** > 4 weeks of prior treatment with IFN or RBV within 6 months prior to randomisation;ALT > 5 x ULN; total bilirubin > 34 µmol/L (> 2 mg/dL) or direct bilirubin > ULN; international normalisation ratio > 1.7; confirmed creatinine clearance < 50 mL/min; or concurrent diagnosis of chronic hepatitis B infection, HIV infection, HCC or other non-HCV liver disease.
Interventions	**Experimental group:** oral 75 mg or 150 mg of beclabuvir twice daily for 48 weeks. **Control group:** placebo.

Tatum 2015a1 *(Continued)*

	Co-intervention: once-weekly subcutaneous peg-IFN (180 lg) and twice-daily oral RBV (weight-based dosing of 1000 mg/day (< 75 kg) or 1200 mg/day (> 75 kg)).
Outcomes	HCV RNA, safety assessment, pharmacokinetics.
Notes	We emailed Tatum and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Tatum 2015a2

Methods	For characteristics see Tatum 2015a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Tatum 2015a2 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as being double-blinded but it was unclear how the blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were assessed
Vested-interest bias	High risk	Bristol-Myers Squibb
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Vierling 2011

Methods	Randomised clinical trial
Participants	111 participants **Sex:** 64 men, 47 women **Mean age:** 46 years **Inclusion criteria:** adults with chronic hepatitis C genotype 1 with no previous treatment for chronic hepatitis C, 18-55 years of age, weight between 40 kg and 125 kg, liver biopsy within 2 years of screening with histology consistent with chronic hepatitis C and no evidence of bridging fibrosis or cirrhosis, participant and participant's partner(s) must each agree to use acceptable methods of contraception for at least 2 weeks prior to Day 1 and continue until at least 6 months after last dose of study drugs and participants must be willing to give written informed consent. **Exclusion criteria:** prior treatment for hepatitis C other than herbal remedies, HIV-positive or known to be co-infected with hepatitis B, medically significant gallbladder or hepatobiliary findings on screening ultrasound, use of any known significant inducers or substrates of CYP3A4 2 weeks prior to start of study medications, use of herbal supplements (milk thistle permitted), diabetic and hypertensive participants with clinically significant ocular examination findings, current moderate or severe depression, history of depression associated with any of the following: hospitalisation for depression, electroconvulsive therapy for depression, depression that resulted in a prolonged absence from work and/or significant disruption of daily functions, suicidal or homicidal ideation and/or attempt, history of severe psychiatric disorders, past history or current use of lithium, clinical diagnosis of substance abuse of alcohol, intravenous drugs, inhalational (not including marijuana), psychotropics, narcotics, cocaine use, prescription or over-the-counter drugs within 5 years of Day 1, past or current use of opiate agonist substitution therapy, any known pre-existing medical condition (CNS, cardiac, pulmonary, immune mediated) that could interfere with the participant's participation in and completion of the

Vierling 2011 *(Continued)*

	study, active clinical gout within the last year, haemoglobinopathy or coagulopathy, myelodysplastic syndromes, organ transplants other than cornea and hair, poor venous access that precluded routine peripheral blood sampling or an indwelling venous catheter, participants with a history of gastric surgery (e.g. stapling, banding, bypass) or participants with a history of malabsorption disorders (e.g. celiac sprue disease), evidence of active or suspected malignancy, or a history of malignancy, within the last 5 years (except adequately treated basal cell carcinoma of the skin). Participants under evaluation for malignancy were not eligible, participants who were pregnant or nursing, participants who intended to become pregnant during the study period and male participants with partners who were, or intended to become, pregnant during the study period.
Interventions	**Experimental group:** 1. narlaprevir 100 mg twice a day and ritonavir 100 mg. 2. narlaprevir 200 mg once a day and ritonavir 100 mg. 3. narlaprevir 400 mg once a day and ritonavir 100 mg. 4. narlaprevir 200 mg once a day and ritonavir 100 mg. There was a 4-week run in with peg-IFN and RBV. 5. narlaprevir 400 mg once a day and ritonavir 100 mg. There was a 4-week run in with peg-IFN and RBV. **Control group:** no intervention. **Co-intervention:** peg-IFN α-2b (1.5 µg/kg subcutaneously, weekly) and RBV (600 mg-1400 mg/d based on weight) for 48 weeks.
Outcomes	Antiviral effects, pharmacokinetics, safety.
Notes	Participants from the control group were allowed to cross over to the experimental group after 12 weeks of treatment. We could therefore only use results from the first 12 weeks. We contacted trial authors about allocation sequence generation and concealment, how was missing data accounted for, SAE, number randomised to each group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Described as open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Above 5% dropouts in the control group and it was unclear how the trial handled missing data
Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol were reported on (NCT00797745)
Vested-interest bias	High risk	The trial was funded by a company that might have an interest in a given result (Merck Sharp & Dohme Corp.)

Vierling 2011 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Villano 2007

Methods	Randomised clinical trial
Participants	Adults with chronic hepatitis C who were naive to treatment
Interventions	**Experimental group:** 1. HCV-796 every 12 h for 14 days + peg-IFN 2b 1.5 µg/kg/week. 2. HCV-796 + peg-IFN 2a 180 µg/week. **Control group:** Control 1: placebo HCV-796 + peg-IFN 2b. Control 2: placebo HCV-796 + peg-IFN 2a.
Outcomes	Antiviral activity
Notes	We contacted trial authors for additional information on allocation sequence generation and concealment, how was blinding maintained, were outcome assessment blinded, how many dropped out, how many were randomised to each group, SVR, death, SAE, prepublished protocol, how was the trial funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind but it was unclear how the blinding was maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear how many participants dropped out
Selective reporting (reporting bias)	Unclear risk	No protocol could be found
Vested-interest bias	High risk	Multiple authors were employees of Wyers

Villano 2007 *(Continued)*

Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Vince 2014

Methods	Randomised clinical trial
Participants	64 adult participants **Sex:** 36 men, 28 women **Mean age:** 45 years **Country:** USA **Inclusion criteria:** male or female participants 18–65 years old inclusive, with a BMI of 18–35 kg/m2; documented clinical history compatible with chronic HCV, including positive anti-HCV antibody, presence of HCV RNA in the plasma for at least 6 months or liver biopsy within 24 months with histology consistent with chronic HCV infection; HCV genotype 1, 2, 3 or 4; plasma HCV RNA P5 log10 IU/mL; all participants agreed to use double-barrier birth control (such as a condom plus spermicide) from screening through at least 90 days following the last dose of the study drug. **Exclusion criteria:** pregnancy or breastfeeding; co-infection with HBV or HIV; history or evidence of decompensated liver disease; prior clinical or histological evidence of cirrhosis; ALT or AST level > 3.0 ULN; history of HCC or findings suggestive of possible HCC; 1 or more additional known primary or secondary causes of liver disease, other than HCV; previous antiviral treatment for HCV; current abuse of alcohol or illicit drugs; or other clinically significant diseases that, in the opinion of the investigator, would jeopardise the safety of the participant or impact the validity of the study results.
Interventions	**Experimental group:** oral 25 mg, 50 mg, 100 mg of samatasvir once a day for 3 days, or 50 mg of samatasvir twice a day for 3 days. **Control group:** placebo.
Outcomes	Safety assessment, pharmacokinetics, antiviral activity, NS5A sequence analysis.
Notes	We emailed Vince and colleagues on 27 April 2016 for additional information but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomisation code were "kept blinded to participants and clinical investigators" and matching placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation code were "kept blinded to participants and clinical investigators" and matching placebo was used

Vince 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts
Selective reporting (reporting bias)	High risk	The primary outcomes were changed (NCT01508156)
Vested-interest bias	High risk	Idenix Pharmaceuticals, Inc
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Wedemeyer 2013

Methods	A phase IIb, randomised, double-blind, active-controlled, parallel-group trial (PROPEL) (NCT00869661)
Participants	424 participants **Sex:** 255 men (60.1%), 169 women (39.9%) Location**:** North America, Europe, and Australia. **Inclusion criteria:** participants with chronic hepatitis C infection genotype 1 or 4, age 18-65 years, treatment-naive, serum HCV RNA level of at least 50,000 IU/mL, liver biopsy consistent with chronic hepatitis C obtained within 24 calendar months before first dose of study drug (36 months for participants with cirrhosis or incomplete/transition to cirrhosis, fibrosis score 3-4). Participants with fibrosis score 3-4 were required to have had an abdominal ultrasound, computerised tomography scan, or magnetic resonance imaging scan without evidence of HCC (within 2 months prior to randomisation) and a serum alfa-fetoprotein < 100 ng/mL. **Exclusion criteria:** hepatitis A or B co-infection, HIV co-infection, history or evidence of other chronic liver disease other than HCV, history or evidence of decompensated liver disease, absolute neutrophil count < 1.5 x 10^9 cells/L, haemoglobin concentration < 12 g/dL in women and < 13 g/dL in men. Platelet count < 90 x 10^9 cells/L, history of renal disease, serum creatinine > 1.5 times the ULN, BMI < 18 or ≥ 36 kg/m^2. Pregnant or breastfeeding women and male partners of pregnant women, inadequate forms of contraception in women of childbearing age and men with female partners of childbearing age (2 forms of contraception required). **Group A:** 80 participants Mean age: 47 years (range 18-62) Race, n(%): white: 70(88), black: 8(10), other: 2(3) HCV genotype, n(%): 1a: 44(55), 1b: 28(35), 4: 8(10) Cirrhosis, n(%): 17(21) **Group B:** 81 participants Mean age: 47 years (range 23-62) Race, n(%): white: 69(85), black: 9(11), other: 3(4) HCV genotype, n(%): 1a: 51(63), 1b: 26(32), 4: 4(5) Cirrhosis, n(%): 18(22) **Group C:** 82 participants

Wedemeyer 2013 *(Continued)*

	Mean age: 47 years (range 21-65) Race, n(%): white: 70(85), black: 9(11), other: 3(4) HCV genotype, n(%): 1a. 50(61), 1b: 26(32), 4: 6(7) Cirrhosis, n(%): 18(22) **Group D:** 81 participants Mean age: 48 years (range 23-60) Race, n(%): white: 71(88), black: 6(7), other: 4(5) HCV genotype, n(%): 1a: 56(69), 1b: 22(27), 4: 3(4) Cirrhosis, n(%): 23(28) **Group E:** 84 participants Mean age: 48 years (range 22-65) Race, n(%): white: 75(89), black: 3(4), other: 6(7) HCV genotype, n(%): 1a: 52(62), 1b: 25(30), 4: 7(8) Cirrhosis, n(%): 19(23).
Interventions	**Experimental group:** Group A: oral mericitabine 500 mg twice daily for 12 weeks. Group B: oral mericitabine 1000 mg twice daily for 8 weeks. Group C: oral mericitabine 1000 mg twice daily for 12 weeks. Group D: oral mericitabine 1000 mg twice daily for 12 weeks. **Control group:** Group E: matched placebo orally twice daily for 12 weeks. **Co-interventions:** Groups A, B, and C: peg-IFN alfa-2a 180 µg subcutaneously once weekly for 24 weeks ifeRVR achieved, or for 48 weeks if eRVR not achieved. Weight-based oral RBV 1000 mg1-200 mg daily in 2 divided doses for 24 weeks if eRVR achieved, or for 48 weeks if eRVR not achieved (eRVR was defined as undetectable HCV RNA (< 15 IU/mL) by week 4 and maintained through week 22). Groups D and E: peg-IFN α-2a 180 µg subcutaneously once weekly for 48 weeks. Weight-based oral RBV 1000 mg-1200 mg daily in 2 divided doses for 48 weeks.
Outcomes	**Primary outcome:** SVR at week 24 after the last dose of study medication. **Secondary outcomes:** viral responses at clinic visits (HCV RNA was determined at baseline and at weeks 1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48 of treatment and at weeks 4, 12, and 24 of follow-up). Proportion of participants with relapse.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Wedemeyer 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was stratified by geographical region and the randomization sequence was generated centrally by the sponsor...The randomization list was not available to personnel at the study centers or to the sponsor's monitors during the study."
Allocation concealment (selection bias)	Low risk	Quote: "...were randomized in enrollment order by central interactive voice-response system or interactive web response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A mericitabine-matched placebo was used. Quote: "Patients and investigators remained blinded to individual treatment assignments during 24/48 weeks of study treatment and 24 weeks of study follow-up."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The randomization list was made available to selected individuals from the sponsor at the time of Data Monitoring Committee review of ˜50% of patients in Cohort 2 at week 12, an independent statistician at the sponsor for analysis of ongoing safety data and an independent medical officer to review interim analysis data."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for withdrawal have been clearly stated.
Selective reporting (reporting bias)	Low risk	The protocol was published prior to randomisation and all pre-specified outcomes were reported on.
Vested-interest bias	High risk	Trial funded by Hoffmann-LaRoche Ltd.
Other bias	Low risk	The trial appeared to be free of other bias domains that could put it at risk of bias.

Wilfret 2013

Methods	Randomised clinical trial
Participants	23 adult participants **Sex:** 20 men, 3 women **Mean age:** 51.5 years **Country:** USA **Inclusion criteria:** chronic HCV (for 6 months) were eligible if they were treatment-naive and noncirrhotic with HCV RNA levels of > 100,000 IU/mL **Exclusion criteria:** infected with HIV, HBV.
Interventions	The trial was divided into 5 cohorts **Experimental group:** oral 1 mg, 10 mg, 30 mg, 60 mg, 120 mg in a single dose of GSK2336805. **Control group:** placebo.
Outcomes	Safety analysis, pharmacokinetics, metabolite identification, clinical virology assessment.
Notes	We emailed Wilfret and colleagues on 27 April 2016 for additional information but reply not received yet.

Wilfret 2013 *(Continued)*

	The study included healthy volunteers.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was described that the trial was double-blinded but it was unclear how the blinding of participants and personnel was performed
Blinding of outcome assessment (detection bias) All outcomes	High risk	Those performing the outcome assessment were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% dropped out
Selective reporting (reporting bias)	High risk	The order of the primary outcomes were changed
Vested-interest bias	High risk	The trial was funded by GlaxoSmithKline
Other bias	Low risk	The trial appeared to be free of other components that could put it at risk of bias

Younossi 2015

Methods	Parallel-group, randomised, placebo-controlled (SIRIUS)
Participants	154 participants **Sex:** 114 men, 40 women **Mean age:** 56.5 (SD 9.2) years **Country:** USA **Inclusion criteria:** treatment-experienced chronic hepatitis C participants with genotype 1. Compensated cirrhosis.
Interventions	**Experimental group:** ledipasvir and sofosbuvir for 24 weeks **Control group:** placebo for 12 weeks, followed by ledipasvir, sofosbuvir, and RBV for 12 weeks.
Outcomes	Not stated.
Notes	Published only as abstract. We emailed Younossi and colleagues on 27 April 2016 for additional information number of participants randomised per group, random sequence generation, method of allocation concealment, description

Younossi 2015 *(Continued)*

of blinding procedure, blinding of outcome assessors, potential number and reasons for drop-outs, pre-defined outcomes, sponsorship and its role, race and ethnicity of participants, full text or at least the figure published in the abstract, and data from quality-of-life assessment but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated that trial was randomised, but method of sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was unclear if participants and treatment providers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not mentioned if the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided
Vested-interest bias	Unclear risk	It was uncertain how the trial was sponsored
Other bias	Low risk	The trial may or may not have been free of other domains that could put it at risk of bias

Zeuzem 2011a

Methods	A randomised, double-blind, placebo-controlled, parallel-group, phase III trial (REALIZE) (NCT00703118)
Participants	662 participants Location**:** Europe, South America, and North America **Inclusion criteria:** age between 18 and 70 years, chronic hepatitis C infection, HCV genotype 1, HCV RNA level ≥ 1000 IU/mL, previously treated, but not achieving SVR, a liver biopsy within 18 months before screening, absolute neutrophil count ≥ 1200 cells/mm^3, platelet count ≥ 90,000 cells/mm^3, haemoglobin level ≥ 12 g/dL for women, and ≥ 13 g/dL for men **Exclusion criteria:** decompensated liver disease, other causes of significant liver disease, other severe active diseases **Group 1:** 266 participants (T12PR48) Sex: 183 men 83 women Mean age: 51 years (range 23-69)

Zeuzem 2011a *(Continued)*

	Race, n(%): white: 246(92), black: 11(4), Asian or other: 9(3) HCV genotype, n(%): 1a: 118(44), 1b: 121(45), 1c: 0, unknown: 27(10) HCV RNA ≥ 800,000 IU/mL, n(%): 238(89) Stage of fibrosis or cirrhosis, n(%): no or minimal fibrosis: 51(19), portal fibrosis: 83(31), bridging fibrosis: 60(23), cirrhosis: 72(27). **Group 2:** 264 participants (lead-in T12PR48) Sex: 189 men, 75 women Mean age: 51 years (range 24-70) Race, n(%): white: 252(95), black: 8(3), Asian or other: 4(2) HCV genotype, n(%): 1a: 121(46), 1b: 115(44), 1c: 0, unknown: 28(11) HCV RNA ≥ 800,000 IU/mL, n(%): 234(89) Stage of fibrosis or cirrhosis, n(%): no or minimal fibrosis: 68(26), portal fibrosis: 71(27), bridging fibrosis: 58(22), cirrhosis: 67(25). **Control group:** 132 participants (PR48) Sex: 88 men, 44 women Mean age: 50 years (range 21-69) Race, n(%): white: 117(89), black: 11(8), Asian or other: 4(3) HCV genotype, n(%): 1a: 59(45), 1b: 59(45), 1c: 1(1), unknown: 13(10) HCV RNA ≥ 800,000 IU/mL, n(%): 114(86) Stage of fibrosis or cirrhosis, n(%): no or minimal fibrosis: 35(27), portal fibrosis: 38(29), bridging fibrosis: 29(22), cirrhosis: 30(23).
Interventions	**Experimental group:** 1. oral telaprevir 750 mg every 8 h for 12 weeks. 2. oral telaprevir 750 mg every 8 h for 12 weeks, beginning at week 5. **Control group:** placebo. **Co-interventions:** peg-IFN α-2a 180 µg subcutaneously once weekly and oral weight-based RBV 1000 mg-1200 mg in 2 divided daily doses for 48 weeks.
Outcomes	**Primary outcome:** proportion of participants with SVR at week 24 (undetectable HCV RNA 24 weeks after end of treatment). **Secondary outcomes:** effect of lead-in treatment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with the use of a centralized system according to a predefined randomization list, constructed through random permuted blocks..."

Zeuzem 2011a *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation concealment was obtained by use of an interactive voice-response/web-response system (IVRS/IWRS). Treatment codes were assigned by the system to the participants, and all codes were kept by IVRS/IWRS and could only be broken by contacting the IVRS/IWRS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A telaprevir-matching placebo was used. All participants and study personnel and sponsor were unaware of treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Results of HCV RNA tests up to week 24 were masked and were monitored by an independent reviewer to assess whether participants had met a predefined stopping rule..."
Incomplete outcome data (attrition bias) All outcomes	High risk	Number and reasons for discontinuation were clearly stated. However, the discontinuation rate was very high, from 30%-38% in the experimental groups, up to 62% in the control group. A majority of participants in the experimental groups discontinued treatment due to AEs, while the main reason for discontinuation in the control group was reaching the virologic stopping rule
Selective reporting (reporting bias)	Low risk	The study protocol was available and all pre-specified outcomes were reported on
Vested-interest bias	High risk	The sponsor (Janssen) was directly involved in trial design and protocol development, as well as editorial assistance in the preparation of the manuscript
Other bias	Low risk	Trial seems to be free of other potential sources of bias

Zeuzem 2014a

Methods	A phase III, randomised, placebo-controlled, double-blind, parallel-group trial (SAPPHIRE-II) (NCT01715415)
Participants	394 participants **Sex:** 227 men, 167 women Location**:** Australia, North America, and Europe **Inclusion criteria:** age between 18 and 70 years, prior null-responder, partial responder, or relapser to peg-IFN/RBV treatment. Chronic hepatitis C HCV genotype 1, no cirrhosis, HCV RNA level > 10,000 IU/mL **Exclusion criteria:** recent history of drug or alcohol abuse (within 6 months prior to study drug administration), HVB or HIV co-infection, history of uncontrolled seizures, history of uncontrolled diabetes, active malignancy or history of malignancy, ALT > 5 x ULN, AST > 5 x ULN, calculated creatinine clearance < 60 mL/min, albumin < lower limit of normal (LLN), prothrombin time/international normalised ratio > 1.5, haemoglobin < LLN, platelets < 120,000 cells per mm^3, absolute neutrophil count < 1500 cells/µL, indirect bilirubin > 1.5 ULN and direct bilirubin > ULN **Group 1:** 297 participants Sex: 167 men, 130 women Mean age: 51.7 years (range: 19.0-71.0) Race, n(%): white: 269(90.6), black: 22(7.4), Asian: 6(2.0) Fibrosis score F2-F3, n(%): 95(32.0)

Zeuzem 2014a *(Continued)*

	IL28B genotype CC, n(%): 34(11.4) HCV genotype, n(%): 1a: 173(58.2), 1b: 123(41.4) **Group 2:** 97 participants Sex: 60 men, 37 women Mean age: 54.9 years (range 30.0-69.0) Race, n(%): white: 86(88.7), black: 10(10.3), Asian: 0 Fibrosis score F2-F3, n(%): 32(33.0) IL28B genotype CC, n(%): 7(7.2) HCV genotype, n(%): 1a: 57(58.8), 1b: 40(41.2)
Interventions	**Experimental group:** Group 1: ABT-450 orally 150 mg once daily with ritonavir 100 mg once daily and ombitasvir 25 mg once daily for 12 weeks. Dasabuvir orally 250 mg twice daily for 12 weeks **Control group:** Group 2: matching placebos for 12 weeks, followed by an open-label period of 12 weeks' administration of the active treatment **Co-intervention:** oral weight-based RBV 1000 mg-1200 mg in 2 divided daily doses (1000 mg daily if body weight was < 75 kg and 1200 mg daily if body weight was ≥ 75 kg)
Outcomes	**Primary outcome:** SVR 12 weeks after the end of study treatment. AEs **Secondary outcomes:** virological failure during treatment. Post-treatment relapse. Percentage of participants with ALT normalisation at the final treatment visit among participants with ALT > ULN at baseline
Notes	We emailed Zeuzem and colleagues on 27 April 2016 for additional information on SVR for placebo group, normalisation of ALT level after treatment but reply not received yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated schedule
Allocation concealment (selection bias)	Low risk	Allocation was performed "through IRT (interactive response technology) system in order to receive unique study bottle/kit numbers and a unique randomisation number", which was used only by the sponsor for loading treatment assignments into the database.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebos were used identical to study drugs.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent DMC received safety data and provided recommendations. All data were blinded to study all study personnel.

Zeuzem 2014a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Number and reasons for discontinuation were clearly stated.
Selective reporting (reporting bias)	Low risk	Study protocol was published and available before randomisation. All prespecified outcomes were reported on.
Vested-interest bias	High risk	The sponsor (AbbVie) was directly involved in study design, data analyses, drafting the manuscript, and submission for publication.
Other bias	Low risk	Trial seems to be free of other potential sources of bias.

AE: adverse events; **ALT**: alanine aminotransferase;**AST**: aspartate aminotransferase; **BMI**: body mass index; **DAA**: direct-acting antiviral(s); **ECG**: electrocardiogram; **EVR**: early virological response;**eRVR**: extended rapid virological response; **FDA**: Food and Drug Administration; **h**: hour(s); **HBV**: hepatitis B virus; **HCC**: hepatocellular carcinoma; **HCV**: hepatitis C virus; **HCV VL** (viral load); **LLOQ**: lower limit of quantification; **mRNA**: messenger RNA; **IFN**: interferon; **PK**: protein kinase; **P/R**: peg-interferon/RBV; **RBV**: ribavirin; **RNA**: ribonucleic acid; **RVR**: rapid virologic response; **SAE**: serious adverse events; **SVR**: sustained viral response; **vs**: versus; **ULN**: upper limit of normal

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AGATE-I 2015	All arms were treated with DAAs
ALLY 2015	All participants were treated with DAAs
ANNAPURNA 2013	All participants were treated with DAAs
APRICOT 2004	Participants were not treated with DAAs
ATOMIC 2013	All participants were treated with DAAs
ATTAIN 2015	All participants were treated with DAAs
AVIATOR 2015	Not a randomised clinical trial. All participants were treated with DAAs
Basu 2014b	The trial compared same treatment regimens (simeprevir 150 mg and sofosbuvir 400 mg) with concomitant different dosages of RBV (modified doses vs 1000 mg) and different treatment duration (24 weeks vs 16 weeks)
Bathgate 2011	Short review written as 'Clinical opinion' for RESPOND-2 and SPRINT-2 trials
Bognar 2011	A Markov model simulation
Bourgeois 2015	Wrong control (different doses of simeprevir)
C-SURFER 2015	All participants were treated with DAAs
C-WORTHY 2015	All participants were treated with DAAs
Chandra 2006b	Participants were healthy
CONCISE 2013	All participants were treated with DAAs
COSMOS 2014	All participants were treated with DAAs

Study	Reason for exclusion
Di Bisceglie 2014	The trial compared the same treatment in equal or different dosages (telaprevir and VX-222) combined with or without peg-IFN and RBV
Dore 2014	Pooled analysis from two different trials
Dusheiko 2015	Was an analyses of multiple trials. It was not clear which trials the study looked at.
Ferenci 2014	Wrong intervention (trial does not actually compare DAA with placebo/other medical intervention)
Ferrante 2011a	A Markov model projection
Ferrante 2011b	A Markov model projection
Ferrante 2013	A Markov model projection
Foster 2010	Pooled analysis of data from different trials
FOURward 2014	Parallel-group design, no control arm
FUSION 2013	No control arm
Gardner 2014b	Participants were healthy
HCVerso 1 2014	No control group
HCVerso 2 2014	No control group
ION-3 2014	Parallel-group design, no control arm
Jacobson 2013	Pooled analysis from two different trials
Kawada 2015	Wrong control
Liu 2015b	RBV was assessed as active treatment
Lok 2010	Wrong control (different doses of DAA)
Lok 2011	Wrong control (different doses of DAA)
Lok 2012a	Wrong control (different doses of DAA)
Lok 2012b	Wrong control (different doses of DAA)
Lok 2014	Wrong control (different doses of DAA)
MALACHITE-I 2016	Wrong control group (control group received another DAA)
MALACHITE-II 2016	Wrong control group (control group received another DAA)
Manns 2014b	Combined analysis of 3 trials
Manns 2015	Compared the same treatment (ledipasvir/sofosbuvir + RBV) of different duration (12 weeks vs 24 weeks)
Mendez 2014	Not a randomised clinical trial (compared other trials)

Study	Reason for exclusion
Mizokami 2015	Wrong intervention/control (compared RBV vs no RBV)
Molina 2015	Not randomised
Muir 2011	Not randomised
Muir 2015	Not randomised
NEUTRINO 2013	Single-group, open label study
Nishiguchi 2014b	No control group
Nomura 2014	Not randomised
NUCLEAR 2013	Parallel-group design, no control arm
OPTIMIST-1 2015	Parallel-group design, no control group
OPTIMIZE 2013	Wrong control (different time points of telaprevir)
Poordad 2014	The trial compared different treatment durations (12 weeks vs 24 weeks) of the same treatment regimen (ABT-450/r-ombitasvir, dasabuvir, and RBV)
Proulx 2008	Healthy volunteers
Reddy 2011	Combined analysis of three trials
Serfaty 2012	Wrong control (all groups received DAA)
Sulkowski 2011	Retrospective study
Sulkowski 2012a	Wrong intervention/control (The trial compared ribavirin versus no ribavirin). Same as Sulkowski 2014 (NCT01359644)
Sulkowski 2012b	Wrong control group (no groups could be used as control)
Sulkowski 2013d	Trial comparing different dosages of the same DAA
Sulkowski 2014	Wrong intervention/control (compared RBV versus no RBV)
Zeuzem 2012	Study evaluating 5 arms of participants treated with same drug regimen comparing different dosages, treatment durations, and/or RBV co-intervention
Zeuzem 2013	Evaluated different dosages of the same treatment regimen
Zeuzem 2014b	The trial was initially designed as a multicenter, phase 3, randomised, placebo-controlled, double-blind trial of sofosbuvir + RBV vs placebo + RBV. Based on new published information, the protocol was amended and the study was redefined as a descriptive study in which the groups were unblinded, the placebo group was terminated, and the study assessed sofosbuvir + RBV for 12 weeks vs sofosbuvir + RBV for 24 weeks

DAA: direct-acting antivirals; **HCV**: hepatitis C virus; **peg-**IFN: pegylated interferon; **RBV**: ribavirin; **v**s: versus

Characteristics of ongoing studies *[ordered by study ID]*

Izumi 2012

Trial name or title	D-Lite
Methods	Randomised clinical trial
Participants	165 adults with chronic hepatitis C, genotype 1, HCV RNA > 100,000 IU/mL at screening, seronegative for HIV and Hepatitis B surface antigen, liver biopsy within prior 2 years; subjects with compensated cirrhosis can enrol and will be capped at approximately 10%
Interventions	BMS-790052 or BMS-650032
Outcomes	
Starting date	4 March 2011
Contact information	
Notes	NCT01309932

Lawitz 2014b

Trial name or title	A randomised study to evaluate the safety and efficacy of IDX719 in combinations with simeprevir and/or TMC647055/ritonavir with or without ribavirin for 12 weeks in subjects with chronic hepatitis C infection
Methods	Randomised clinical trial
Participants	Treatment-naïve, genotype 1b, 4 and 6 hepatitis C virus-infected participants
Interventions	Samatasvir
Outcomes	
Starting date	6 May 2013
Contact information	
Notes	NCT01852604

DATA AND ANALYSES

Comparison 1. DAA on or on the way to the market versus placebo/no intervention (morbidity or all cause mortality analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hepatitis C-related morbidity or all-cause mortality	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Hepatitis C-related morbidity or all-cause mortality - bias risk	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Trials at high risk of bias	71		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Trials at low risk of bias	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Hepatitis C-related morbidity or all-cause mortality - according to type of DAA	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 ABT-072	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 ACH-2684	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Alisporivir	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 ALS-2200	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Asunaprevir	6		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 Balapiravir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.7 Beclabuvir	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.8 BILB-1941	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.9 BIT-225	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.10 Boceprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.11 Ciluprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.12 Daclatasvir	14		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.13 Danoprevir	9		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.14 Dasabuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.15 Deleobuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.16 Faldaprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.17 Filibuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.18 Grazoprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.19 GS-6620	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.20 GS-9256	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.21 GS-9451	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.22 GS-9669	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.23 GS-9851	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.24 GS-9857	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.25 GSK2336805	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.26 GSK2878175	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.27 IDX-184	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.28 INX-08189	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.29 Ledispasvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.30 Mericitabine	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.31 Narlaprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.32 Nesbuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.33 Odalasavir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.34 Ombitasvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.35 Paritaprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.36 PHX1766	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.37 PPI-461	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.38 PSI-352938	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.39 Samatasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.40 Setrobuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.41 Simeprevir	14		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.42 Sofosbuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.43 Sovaprevir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.44 Tegobuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.45 Telaprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.46 Valopicitabine	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.47 Vaniprevir	9		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.48 VCH-759	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.49 VCH-916	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.50 Velpatasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.51 VX-222	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.52 Mixed	4		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Hepatitis C-related morbidity or all-cause mortality - according to group of DAA	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Cyclophilin	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 NS3/NS4A inhibitors	41		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 NS5B inhibitors (NPI)	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 NS5B inhibitors (NNPI)	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 NS5A inhibitors	18		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 VPU-ion channel inhibitors	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Mixed	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Hepatitis C-related morbidity or all-cause mortality - according to HIV-infection	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 With HIV-infection	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Without HIV-infection	69		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Mixed (with and without HIV-infection)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Unclear	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Hepatitis C-related morbidity or all-cause mortality - according to comorbidity	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 With comorbidity	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Without comorbidity	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Unclear	71		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Hepatitis C-related morbidity or all-cause mortality - according to viral genotype	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Genotype 1	57		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

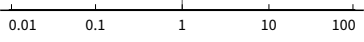
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Genotype 2	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Genotype 3	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Genotype 4	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.5 Mixed	14		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Hepatitis C-related morbidity or all-cause mortality - according to human genotype (IL28b)	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 IL28b (CC)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 IL28B (CT)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 IL28B (TT)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 IL28B (CT + TT)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.5 Mixed	71		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Hepatitis C-related morbidity or all-cause mortality - according to Asian-region	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 From Asian region	8		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Not from Asian region	52		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Mixed	11		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 Unclear	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Hepatitis C-related morbidity or all-cause mortality - according to specific ethnicities	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 White	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Black	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Hispanic	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 Mixed	70		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.5 Unclear	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Hepatitis C-related morbidity or all-cause mortality - according to reaching planned sample size	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Trials reaching planned sample size	10		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 Trials not reaching planned sample size	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Unclear	58		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Hepatitis C-related morbidity or all-cause mortality - according to prior treatment	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 Treatment-naive	47		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Treatment-experienced	16		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Mixed	8		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.4 Unclear	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Hepatitis C-related morbidity or all-cause mortality - according to interferon	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Trials where both groups received interferon	52		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Trials where neither group received interferon	19		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Hepatitis C-related morbidity or all-cause mortality - according to ribavirin	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 Trials where both groups received ribavirin	52		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Trials where neither group received ribavirin	19		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Hepatitis C-related morbidity or all-cause mortality - according to chronic kidney disease	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 With chronic kidney disease	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Without chronic kidney disease	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Unclear	71		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Hepatitis C-related morbidity or all-cause mortality - according to cryoglobulinaemia	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.1 With cryoglobulinaemia	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

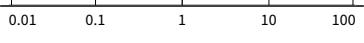
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 Without cryoglobulinaemia	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Unclear	71		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Hepatitis C-related morbidity or all-cause mortality - according to DAA group as co-intervention	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 Trials where DAA were used as co-intervention	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Trials where DAA were not a co-intervention	69		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Hepatitis C-related morbidity or all-cause mortality - according to median dose	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
18.1 Over or equal to median dose	41		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Under median dose	27		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.3 Not available	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 DAA on or on the way to the market versus placebo/no intervention (morbidity or all cause mortality analyses), Outcome 1 Hepatitis C-related morbidity or all-cause mortality.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable



Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable



Favours DAA

Favours control

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Wilfret 2013	0/17	0/6		Not estimable

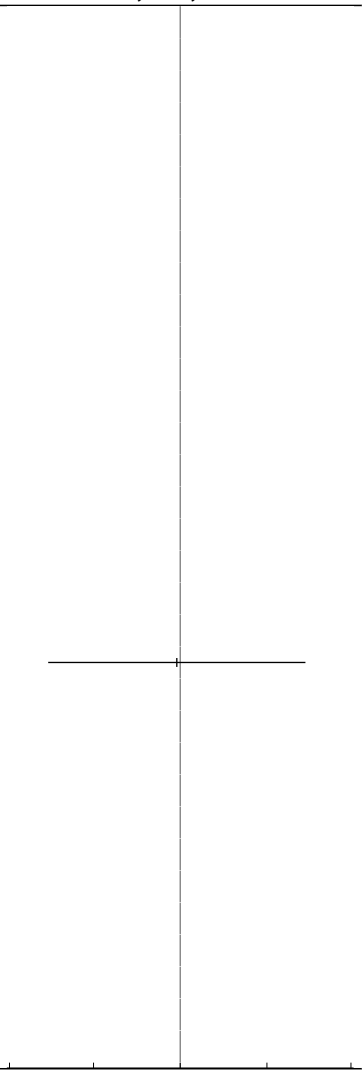
Favours DAA 0.01 0.1 1 10 100 Favours control

Analysis 1.2. Comparison 1 DAA on or on the way to the market versus placebo/no intervention (morbidity or all cause mortality analyses), Outcome 2 Hepatitis C-related morbidity or all-cause mortality - bias risk.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Trials at high risk of bias				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable

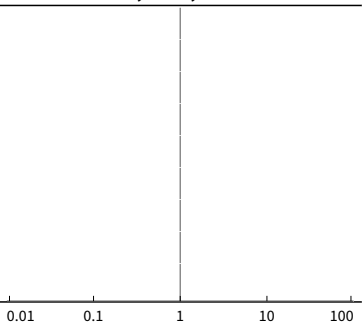
Favours DAA 0.01 0.1 1 10 100 Favours control

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
1.2.2 Trials at low risk of bias				

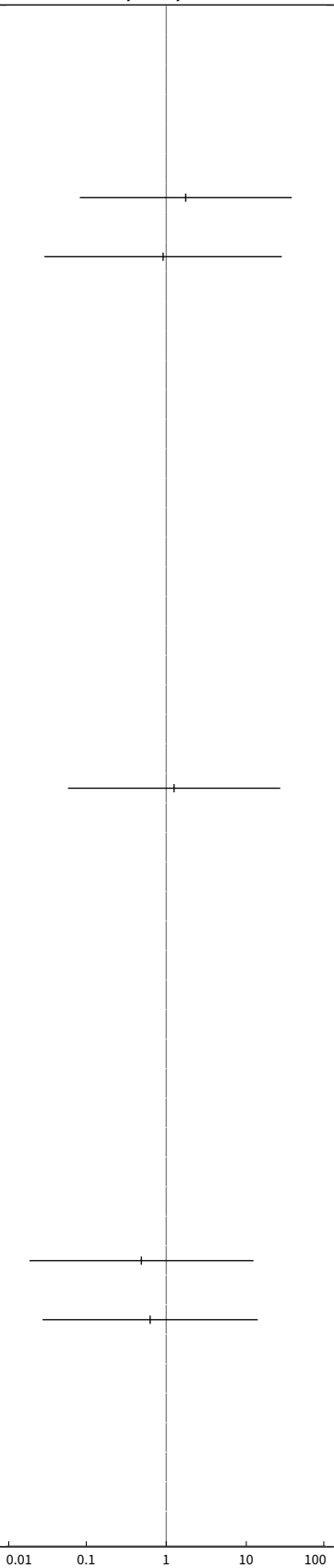


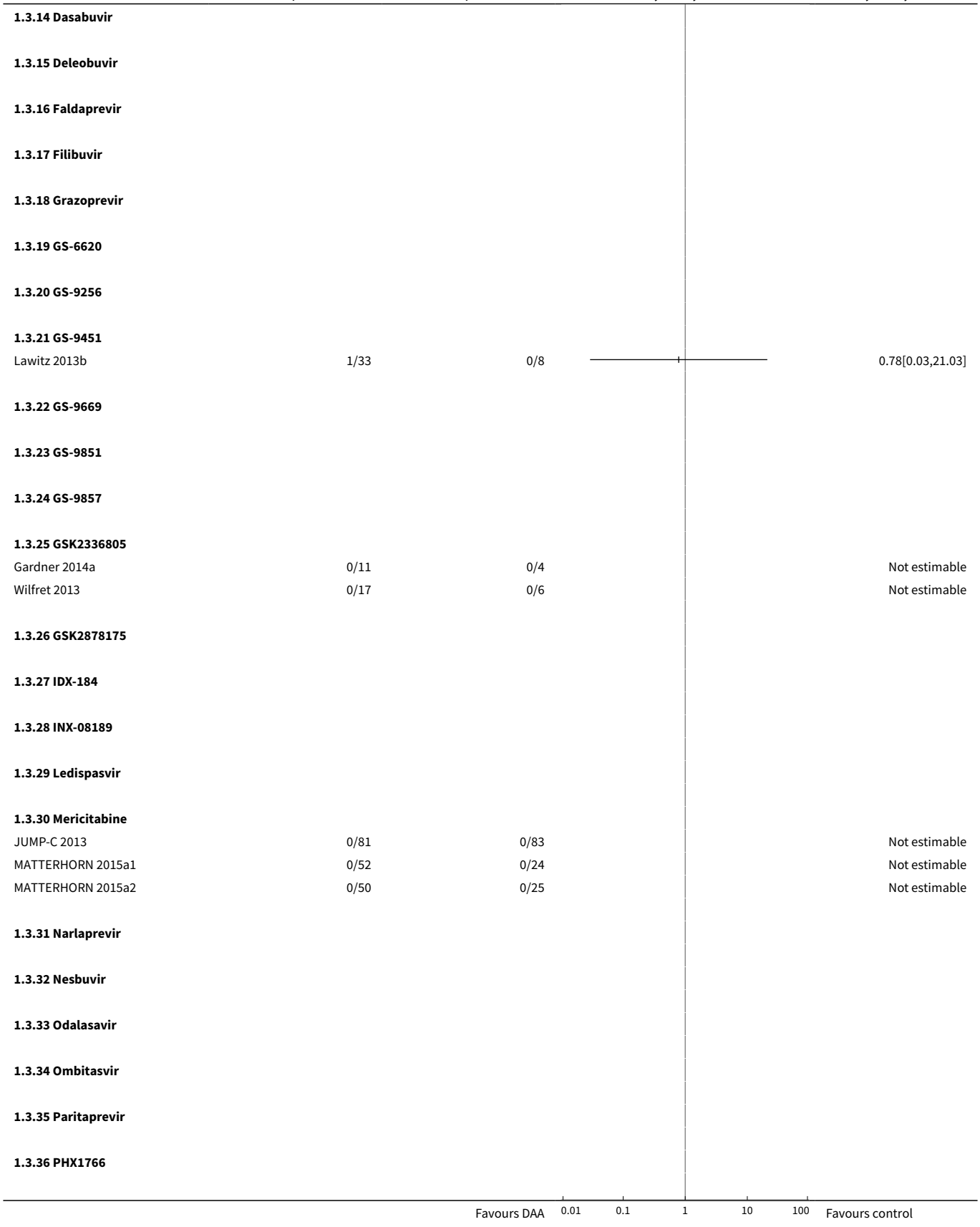
Analysis 1.3. Comparison 1 DAA on or on the way to the market versus placebo/no intervention (morbidity or all cause mortality analyses), Outcome 3 Hepatitis C-related morbidity or all-cause mortality - according to type of DAA.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.3.1 ABT-072				
1.3.2 ACH-2684				
1.3.3 Alisporivir				
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable

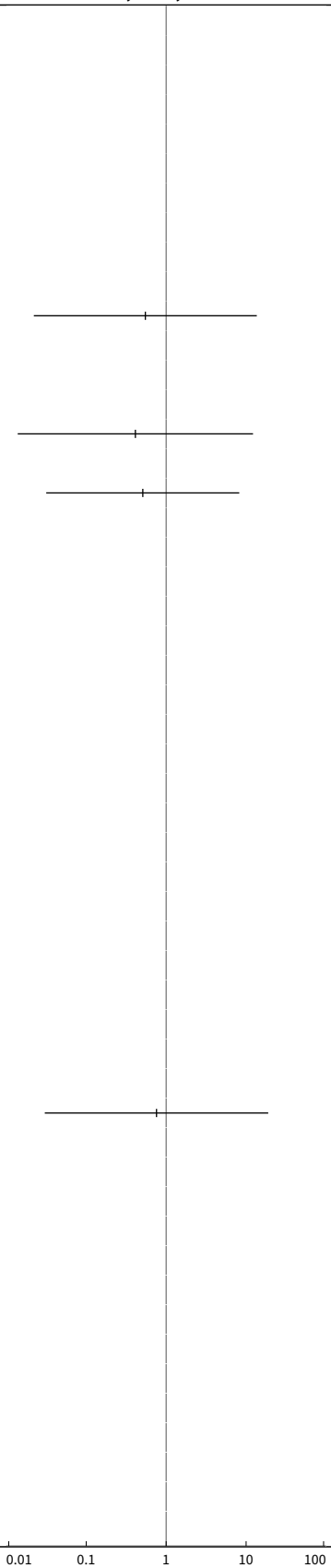


Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.3.4 ALS-2200				
1.3.5 Asunaprevir				
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
1.3.6 Balapiravir				
1.3.7 Beclabuvir				
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
1.3.8 BILB-1941				
1.3.9 BIT-225				
1.3.10 Boceprevir				
1.3.11 Ciluprevir				
1.3.12 Daclatasvir				
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pol 2012	0/36	0/12		Not estimable
1.3.13 Danoprevir				
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Gane 2011	0/25	0/5		Not estimable





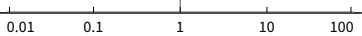
Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.3.37 PPI-461				
1.3.38 PSI-352938				
1.3.39 Samatasvir				
Vince 2014	0/52	0/12		Not estimable
1.3.40 Setrobuvir				
1.3.41 Simeprevir				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
CONCERTO-1 2015	0/123	0/60		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
1.3.42 Sofosbuvir				
1.3.43 Sovaprevir				
Lalezari 2011	0/48	0/15		Not estimable
1.3.44 Tegobuvir				
1.3.45 Telaprevir				
1.3.46 Valopicitabine				
1.3.47 Vaniprevir				
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
1.3.48 VCH-759				
1.3.49 VCH-916				
1.3.50 Velpatasvir				



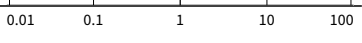
Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2015	0/39	0/17		Not estimable
1.3.51 VX-222				
1.3.52 Mixed				
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Gane 2010	0/57	0/14		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable

Analysis 1.4. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 4 Hepatitis C-related morbidity or all-cause mortality - according to group of DAA.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Cyclophilin				
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
1.4.2 NS3/NS4A inhibitors				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Gane 2011	0/25	0/5		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Manns 2012a1	0/18	0/5		Not estimable

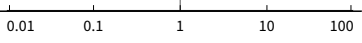


Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
1.4.3 NS5B inhibitors (NPI)				
JUMP-C 2013	0/81	0/83		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
1.4.4 NS5B inhibitors (NNPI)				
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
1.4.5 NS5A inhibitors				
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pol 2012	0/36	0/12		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
1.4.6 VPU-ion channel inhibitors				
1.4.7 Mixed				
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Gane 2010	0/57	0/14		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable

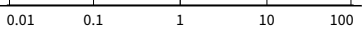


Analysis 1.5. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 5 Hepatitis C-related morbidity or all-cause mortality - according to HIV-infection.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.5.1 With HIV-infection				
1.5.2 Without HIV-infection				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable

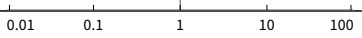


Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
1.5.3 Mixed (with and without HIV-infection)				
1.5.4 Unclear				
Lalezari 2011	0/48	0/15		Not estimable
Nettles 2010	0/16	0/2		Not estimable



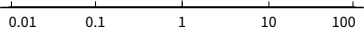
Analysis 1.6. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 6 Hepatitis C-related morbidity or all-cause mortality - according to comorbidity.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.6.1 With comorbidity				
1.6.2 Without comorbidity				
1.6.3 Unclear				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable



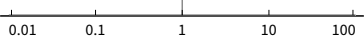
Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable

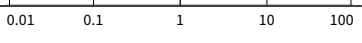


Analysis 1.7. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 7 Hepatitis C-related morbidity or all-cause mortality - according to viral genotype.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.7.1 Genotype 1				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
CONCERTO-1 2015	0/123	0/60		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
Lalezari 2011	0/48	0/15		Not estimable



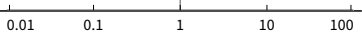
Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
1.7.2 Genotype 2				
1.7.3 Genotype 3				
1.7.4 Genotype 4				
1.7.5 Mixed				
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Gardner 2014a	0/11	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable



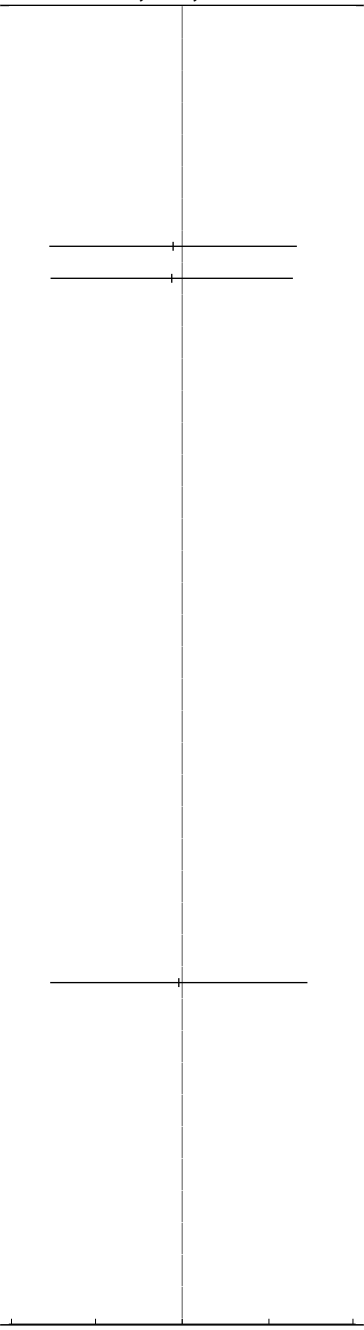
Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2015	0/39	0/17		Not estimable
Vince 2014	0/52	0/12		Not estimable

Analysis 1.8. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 8 Hepatitis C-related morbidity or all-cause mortality - according to human genotype (IL28b).

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.8.1 IL28b (CC)				
1.8.2 IL28B (CT)				
1.8.3 IL28B (TT)				
1.8.4 IL28B (CT + TT)				
1.8.5 Mixed				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable

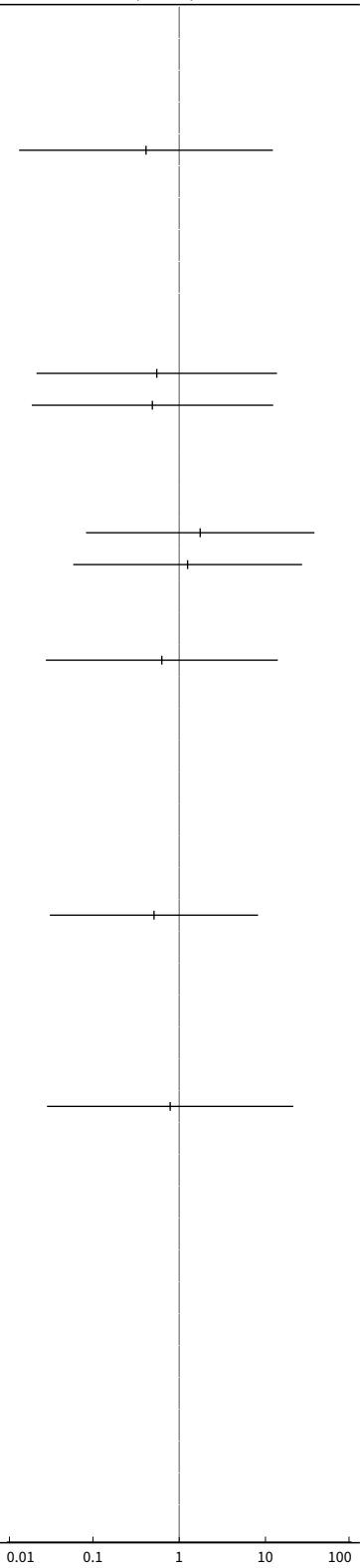


Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable

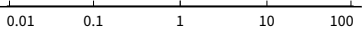


Analysis 1.9. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 9 Hepatitis C-related morbidity or all-cause mortality - according to Asian-region.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.9.1 From Asian region				
CONCERTO-1 2015	0/123	0/60		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Fried 2013	0/309	0/77		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
1.9.2 Not from Asian region				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2015	0/39	0/17		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable

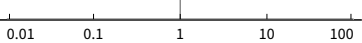


Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
1.9.3 Mixed				
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
1.9.4 Unclear				



Analysis 1.10. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 10 Hepatitis C-related morbidity or all-cause mortality - according to specific ethnicities.

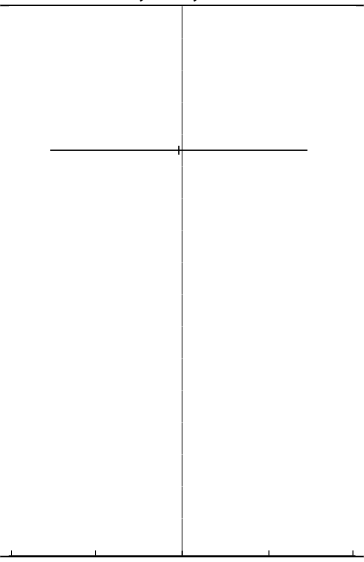
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.10.1 White				
CONCERTO-1 2015	0/123	0/60		Not estimable
1.10.2 Black				
1.10.3 Hispanic				
1.10.4 Mixed				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable

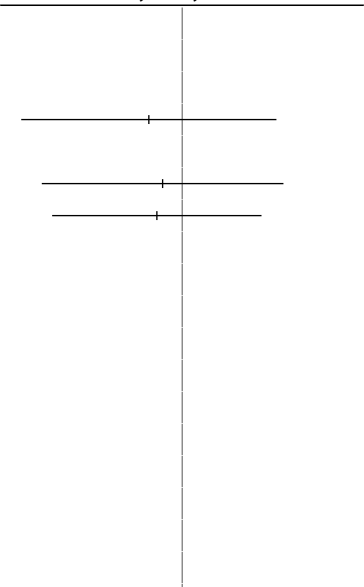
Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
1.10.5 Unclear				

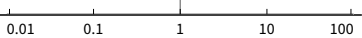


Analysis 1.11. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 11 Hepatitis C-related morbidity or all-cause mortality - according to reaching planned sample size.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.11.1 Trials reaching planned sample size				
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
1.11.2 Trials not reaching planned sample size				
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
1.11.3 Unclear				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]



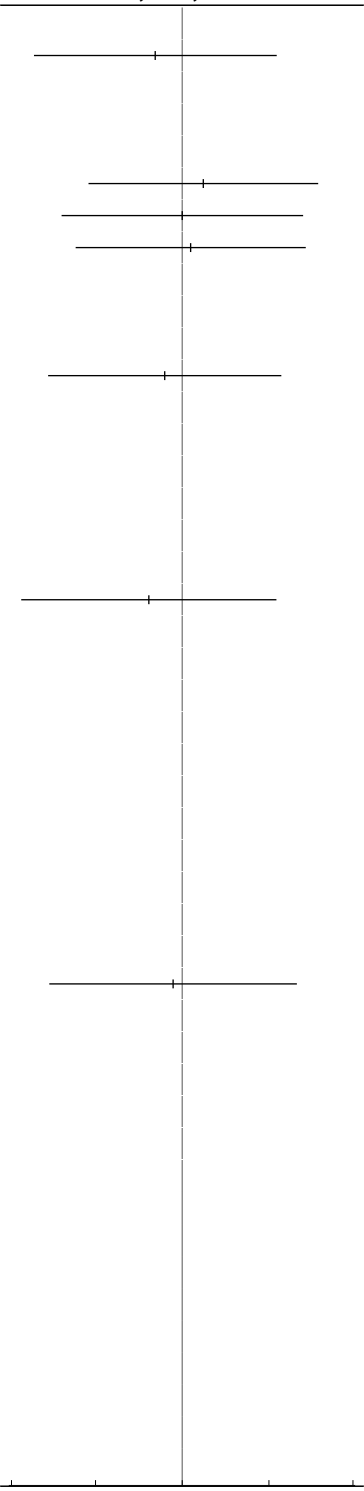
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable



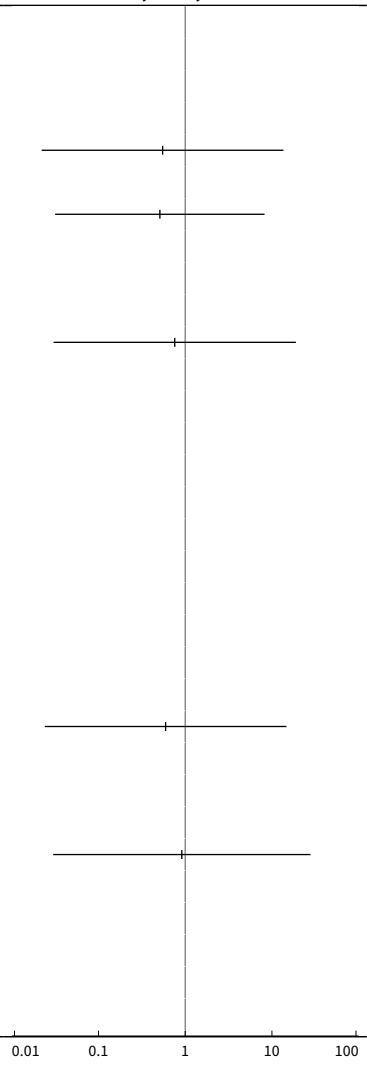
Favours DAAs Favours control

Analysis 1.12. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 12 Hepatitis C-related morbidity or all-cause mortality - according to prior treatment.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.12.1 Treatment-naive				
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Fried 2013	0/309	0/77		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable

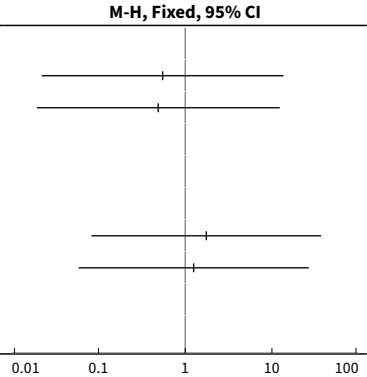


Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Tatum 2015a2	0/13	0/6		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
1.12.2 Treatment-experienced				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
Forestier 2011a2	0/8	0/2		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
1.12.3 Mixed				
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Gane 2010	0/57	0/14		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Sims 2014	0/20	0/4		Not estimable
Vince 2014	0/52	0/12		Not estimable
1.12.4 Unclear				

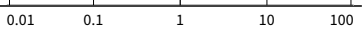


Analysis 1.13. Comparison 1 DAA on or on the way to the market versus placebo/no intervention (morbidity or all cause mortality analyses), Outcome 13 Hepatitis C-related morbidity or all-cause mortality - according to interferon.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.13.1 Trials where both groups received interferon				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
1.13.2 Trials where neither group received interferon				
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2015	0/39	0/17		Not estimable



Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Sims 2014	0/20	0/4		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable

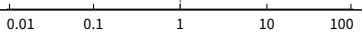
Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 1.14. Comparison 1 DAA on or on the way to the market versus placebo/no intervention (morbidity or all cause mortality analyses), Outcome 14 Hepatitis C-related morbidity or all-cause mortality - according to ribavirin.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.14.1 Trials where both groups received ribavirin				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable

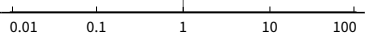
Favours DAAs 0.01 0.1 1 10 100 Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
1.14.2 Trials where neither group received ribavirin				
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2015	0/39	0/17		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Sims 2014	0/20	0/4		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable



Analysis 1.15. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 15 Hepatitis C-related morbidity or all-cause mortality - according to chronic kidney disease.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.15.1 With chronic kidney disease				
1.15.2 Without chronic kidney disease				
1.15.3 Unclear				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable

Favours DAAs 0.01 0.1 1 10 100 Favours control

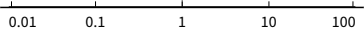
Analysis 1.16. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 16 Hepatitis C-related morbidity or all-cause mortality - according to cryoglobulinaemia.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.16.1 With cryoglobulinaemia				
1.16.2 Without cryoglobulinaemia				
1.16.3 Unclear				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]

Favours DAAs 0.01 0.1 1 10 100 Favours control

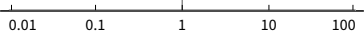
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable

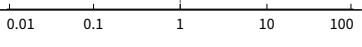


Analysis 1.17. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 17 Hepatitis C-related morbidity or all-cause mortality - according to DAA group as co-intervention.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.17.1 Trials where DAA were used as co-intervention				
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
1.17.2 Trials where DAA were not a co-intervention				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]



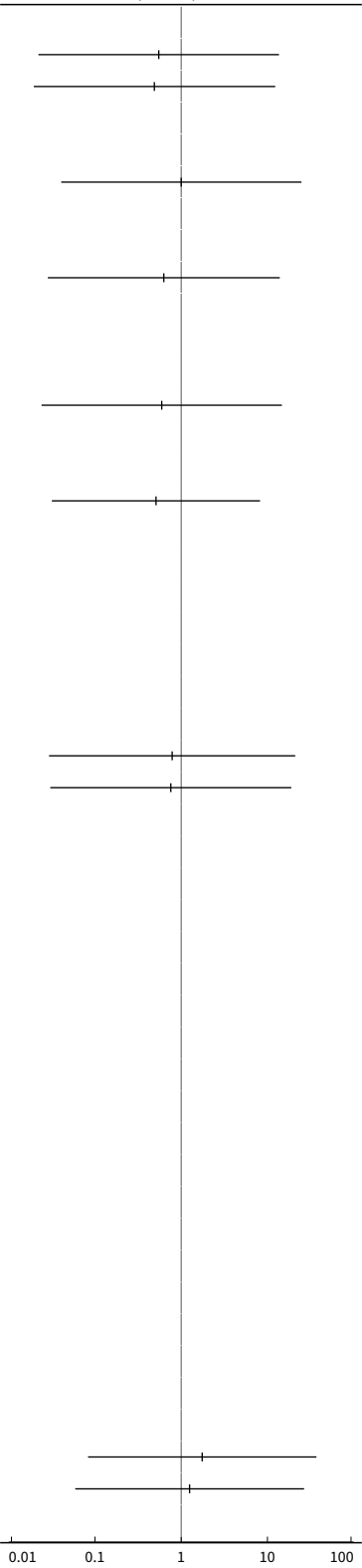
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable



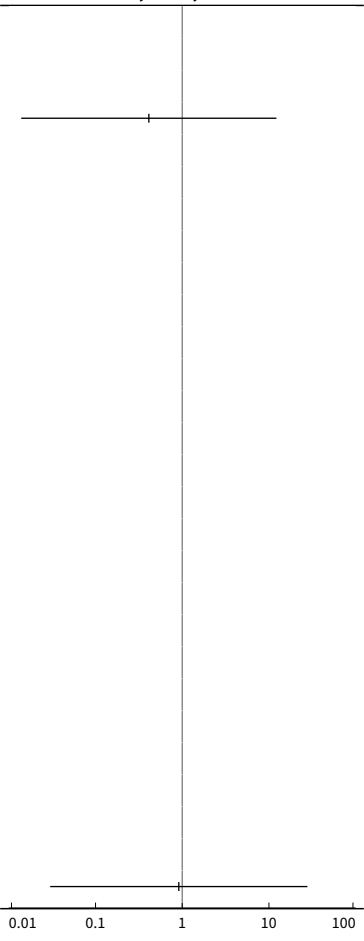
Favours DAAs Favours control

Analysis 1.18. Comparison 1 DAA on or on the way to the market versus placebo/ no intervention (morbidity or all cause mortality analyses), Outcome 18 Hepatitis C-related morbidity or all-cause mortality - according to median dose.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.18.1 Over or equal to median dose				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a2	0/158	0/39		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
1.18.2 Under median dose				
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
CONCERTO-1 2015	0/123	0/60		Not estimable



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dauphine 2015a3	0/94	0/11		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Forestier 2011a1	0/32	0/8		Not estimable
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Gane 2011	0/25	0/5		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
1.18.3 Not available				
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]



Comparison 2. DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Serious adverse events - bias risk	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Trials at high risk of bias	101		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Trials at low risk of bias	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Serious adverse events - according to type of DAA	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 ABT-072	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 ACH-2684	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Alisporivir	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 ALS-2200	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Asunaprevir	6		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 Balapiravir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.7 Beclabuvir	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.8 BILB-1941	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.9 BIT-225	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.10 Boceprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.11 Ciluprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.12 Daclatasvir	14		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.13 Danoprevir	9		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.14 Dasabuvir	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.15 Deleobuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.16 Faldaprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.17 Filibuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.18 Grazoprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.19 GS-6620	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.20 GS-9256	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.21 GS-9451	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.22 GS-9669	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.23 GS-9851	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.24 GS-9857	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.25 GSK2336805	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.26 GSK2878175	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.27 IDX-184	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.28 INX-08189	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.29 Ledispasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.30 Mericitabine	7		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.31 Narlaprevir	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.32 Nesbuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.33 Odalasavir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.34 Ombitasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.35 Paritaprevir	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.36 PHX1766	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.37 PPI-461	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.38 PSI-352938	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.39 Samatasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.40 Setrobuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.41 Simeprevir	18		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.42 Sofosbuvir	4		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.43 Sovaprevir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.44 Tegobuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.45 Telaprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.46 Valopicitabine	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.47 Vaniprevir	10		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.48 VCH-759	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.49 VCH-916	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.50 Velpatasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.51 VX-222	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.52 Mixed	7		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Serious adverse events - according to group of DAA	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Cyclophilin	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 NS3/NS4A inhibitors	56		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 NS5B inhibitors (NPI)	8		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 NS5B inhibitors (NNPI)	5		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 NS5A inhibitors	25		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 VPU-ion channel inhibitors	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Mixed	4		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Serious adverse events - according to HIV-infection	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 With HIV-infection	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Without HIV-infection	94		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Mixed (with and without HIV-infection)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Unclear	7		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Serious adverse events - according to comorbidity	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 With comorbidity	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Without comorbidity	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Unclear	101		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Serious adverse events - according to viral genotype	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Genotype 1	84		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Genotype 2	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Genotype 3	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Genotype 4	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.5 Mixed	17		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Serious adverse events - according to human genotype (IL28b)	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 IL28b (CC)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 IL28B (CT)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 IL28B (TT)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 IL28B (CT + TT)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

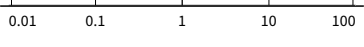
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.5 Mixed	101		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Serious adverse events - according to Asian-region	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 From Asian region	10		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Not from Asian region	76		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Mixed	11		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 Unclear	4		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Serious adverse events - according to specific ethnicities	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 White	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Black	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Hispanic	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 Mixed	101		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.5 Unclear	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Serious adverse events - according to reaching planned sample size	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Trials reaching planned sample size	15		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Trials not reaching planned sample size	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Unclear	83		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Serious adverse events - according to prior treatment	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 Treatment-naive	72		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Treatment-experienced	19		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Mixed	9		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.4 Unclear	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Serious adverse events - according to interferon	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Trials where both groups received interferon	69		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Trials where neither group received interferon	29		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Unclear	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Serious adverse events - according to ribavirin	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 Trials where both groups received ribavirin	73		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Trials where neither group received ribavirin	27		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Unclear	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Serious adverse events - according to chronic kidney disease	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 With chronic kidney disease	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Without chronic kidney disease	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Unclear	101		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Serious adverse events - according to cryoglobulinaemia	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.1 With cryoglobulinaemia	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Without cryoglobulinaemia	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Unclear	101		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Serious adverse events - according to DAA group as co-intervention	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 Trials where DAA were used as co-intervention	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Trials where DAA were not a co-intervention	99		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Serious adverse events - according to median dose	101		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

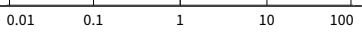
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Over or equal to median dose	58		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Under median dose	37		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.3 Not available	6		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 DAA on or on the way to the market versus placebo/ no intervention (serious adverse events analyses), Outcome 1 Serious adverse events.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable



Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]

Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 2.2. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 2 Serious adverse events - bias risk.

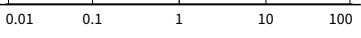
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.2.1 Trials at high risk of bias				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]

Favours DAAs 0.01 0.1 1 10 100 Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]

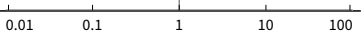
Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.2.2 Trials at low risk of bias				

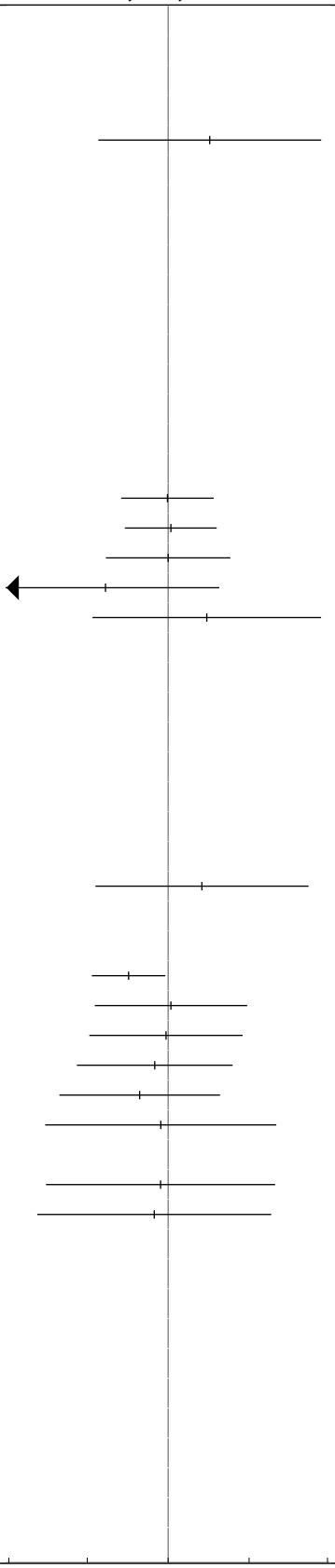


Analysis 2.3. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 3 Serious adverse events - according to type of DAA.

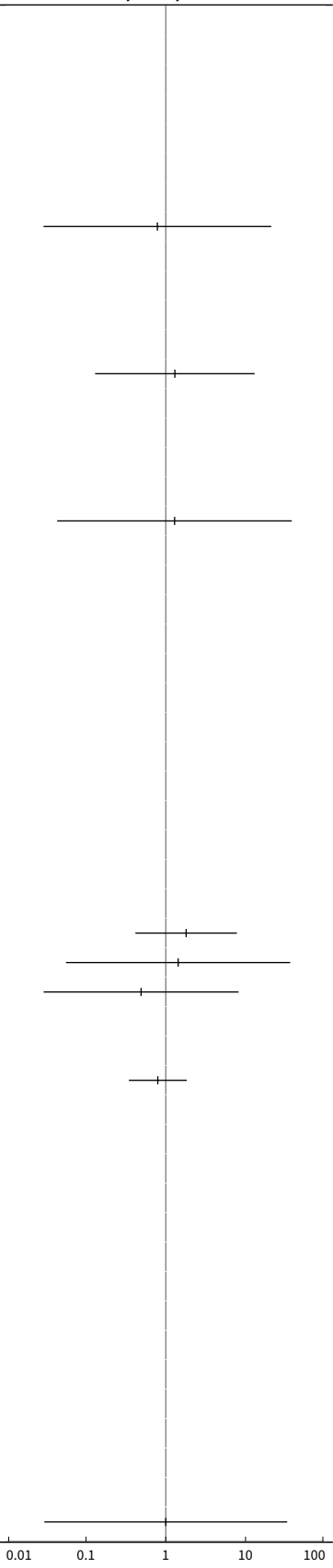
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.3.1 ABT-072				
2.3.2 ACH-2684				
2.3.3 Alisporivir				
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
2.3.4 ALS-2200				
2.3.5 Asunaprevir				
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]



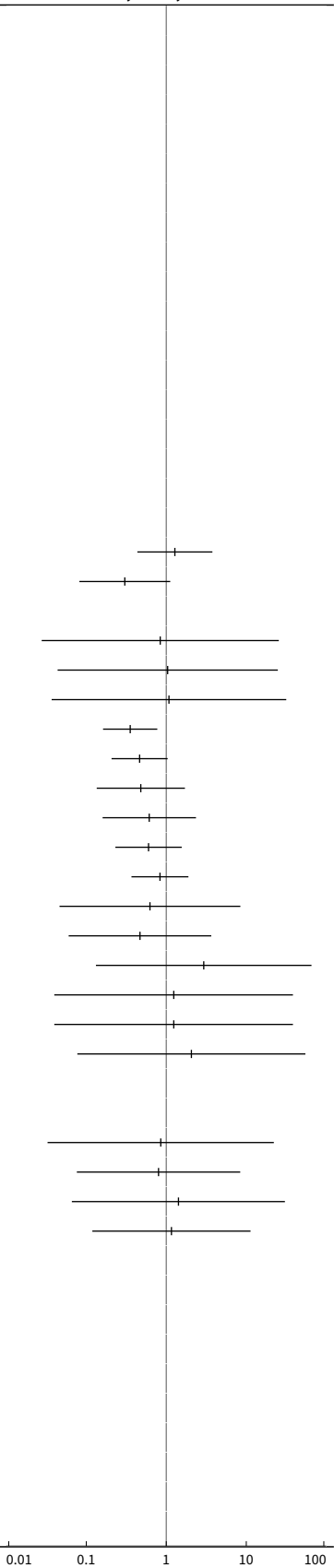
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.3.6 Balapiravir				
2.3.7 Beclabuvir				
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
2.3.8 BILB-1941				
2.3.9 BIT-225				
2.3.10 Boceprevir				
2.3.11 Ciluprevir				
2.3.12 Daclatasvir				
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pol 2012	3/36	0/12		2.61[0.13,54.25]
2.3.13 Danoprevir				
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
2.3.14 Dasabuvir				
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
2.3.15 Deleobuvir				
2.3.16 Faldaprevir				
2.3.17 Filibuvir				



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.3.18 Grazoprevir				
2.3.19 GS-6620				
2.3.20 GS-9256				
2.3.21 GS-9451				
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
2.3.22 GS-9669				
2.3.23 GS-9851				
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
2.3.24 GS-9857				
2.3.25 GSK2336805				
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
Wilfret 2013	0/17	0/6		Not estimable
2.3.26 GSK2878175				
2.3.27 IDX-184				
2.3.28 INX-08189				
2.3.29 Ledispasvir				
Lawitz 2012a	0/59	0/12		Not estimable
2.3.30 Mericitabine				
Gane 2008	0/20	0/5		Not estimable
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
2.3.31 Narlaprevir				
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
2.3.32 Nesbuvir				
2.3.33 Odalasavir				
Gane 2015	0/18	0/12		Not estimable
2.3.34 Ombitasvir				
Sullivan 2012	0/28	0/9		Not estimable
2.3.35 Paritaprevir				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]



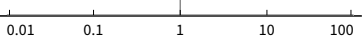
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
2.3.36 PHX1766				
2.3.37 PPI-461				
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
2.3.38 PSI-352938				
2.3.39 Samatasvir				
Vince 2014	0/52	0/12		Not estimable
2.3.40 Setrobuvir				
2.3.41 Simeprevir				
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
2.3.42 Sofosbuvir				
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
2.3.43 Sovaprevir				
Lalezari 2011	0/48	0/15		Not estimable
2.3.44 Tegobuvir				
2.3.45 Telaprevir				
2.3.46 Valopicitabine				



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.3.47 Vaniprevir				
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013e	0/35	0/5		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
2.3.48 VCH-759				
2.3.49 VCH-916				
2.3.50 Velpatasvir				
Lawitz 2015	0/39	0/17		Not estimable
2.3.51 VX-222				
2.3.52 Mixed				
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]

Analysis 2.4. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 4 Serious adverse events - according to group of DAA.

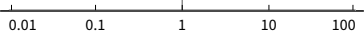
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.4.1 Cyclophilin				
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
2.4.2 NS3/NS4A inhibitors				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013e	0/35	0/5		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.4.3 NS5B inhibitors (NPI)				
Gane 2008	0/20	0/5		Not estimable

Favours DAAs | Favours control

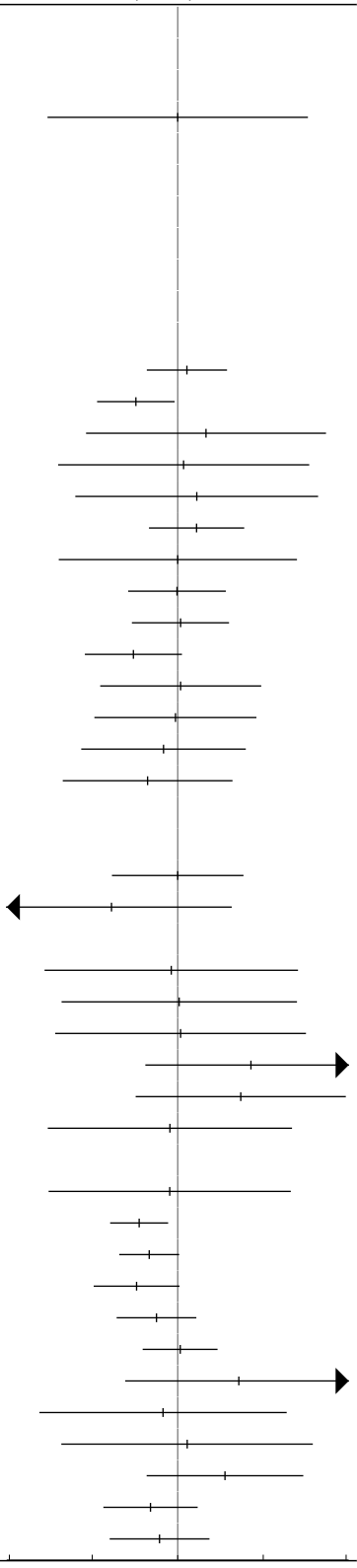
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Reddy 2007	0/32	0/8		Not estimable
2.4.4 NS5B inhibitors (NNPI)				
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
2.4.5 NS5A inhibitors				
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Sullivan 2012	0/28	0/9		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
2.4.6 VPU-ion channel inhibitors				
2.4.7 Mixed				
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]



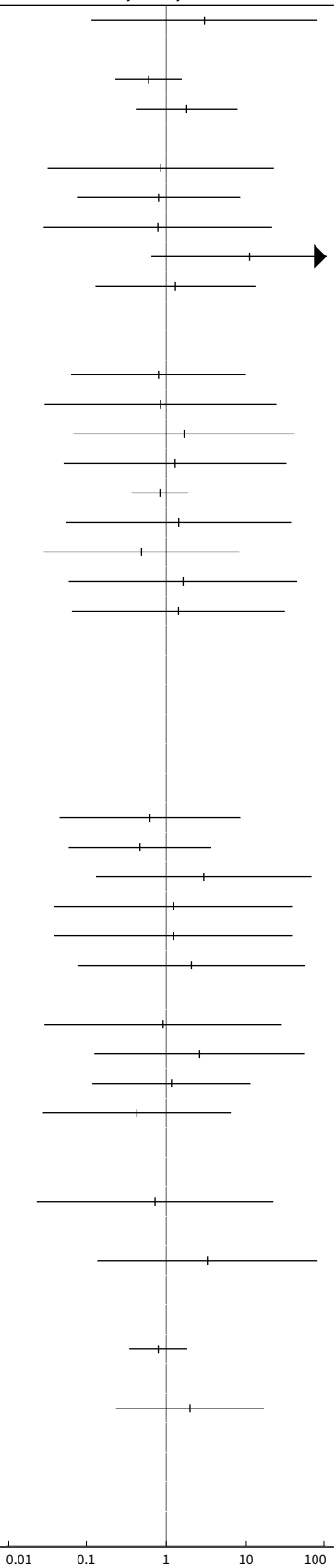
Favours DAAs Favours control

Analysis 2.5. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 5 Serious adverse events - according to HIV-infection.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.5.1 With HIV-infection				
2.5.2 Without HIV-infection				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.5.3 Mixed (with and without HIV-infection)				
2.5.4 Unclear				



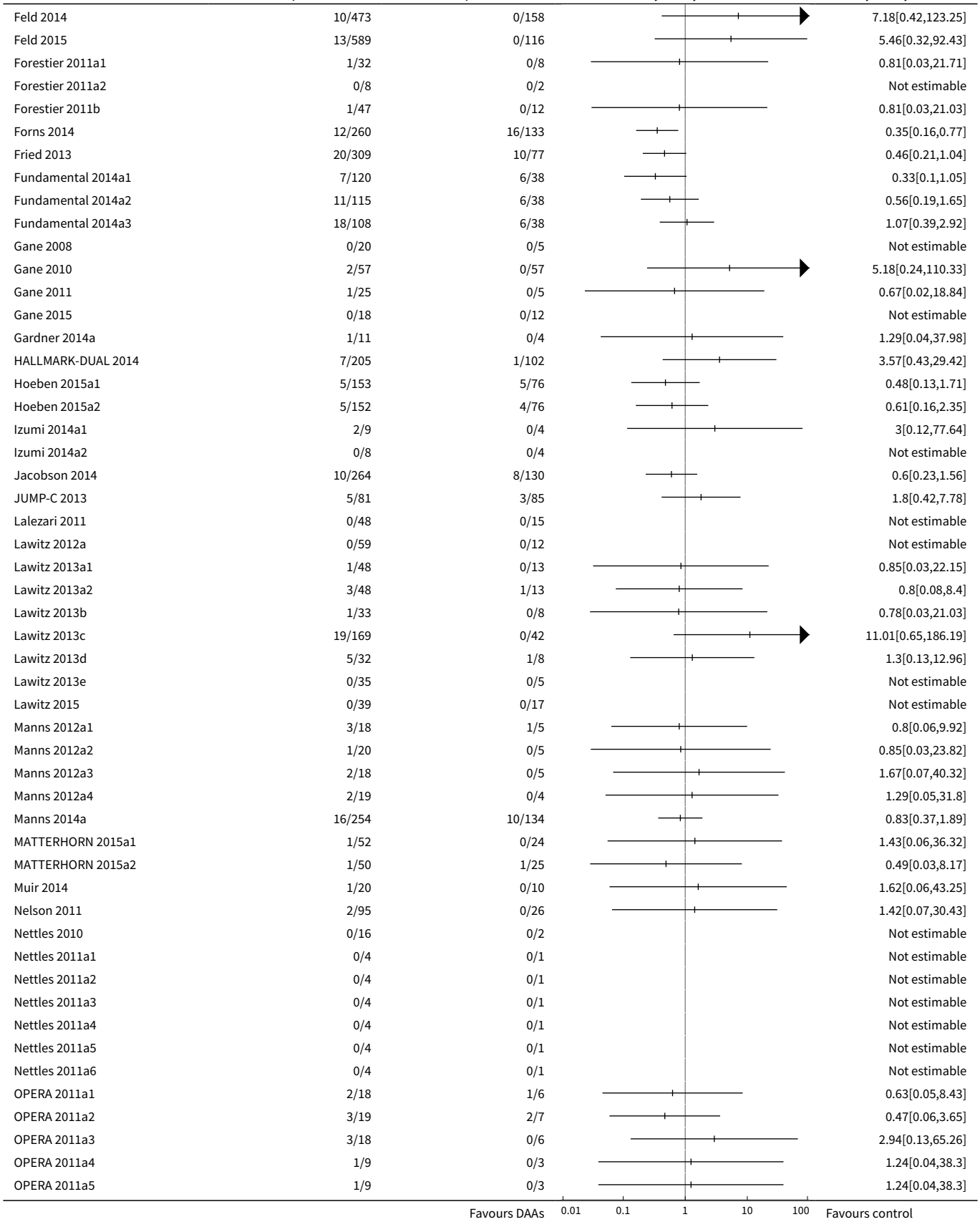
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Gane 2008	0/20	0/5		Not estimable
Gane 2015	0/18	0/12		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Sullivan 2012	0/28	0/9		Not estimable

Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 2.6. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 6 Serious adverse events - according to comorbidity.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.6.1 With comorbidity				
2.6.2 Without comorbidity				
2.6.3 Unclear				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]

Favours DAAs 0.01 0.1 1 10 100 Favours control



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
		Favours DAAs	0.01 0.1 1 10 100	Favours control

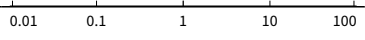
Analysis 2.7. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 7 Serious adverse events - according to viral genotype.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.7.1 Genotype 1				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
		Favours DAAs	0.01 0.1 1 10 100	Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]

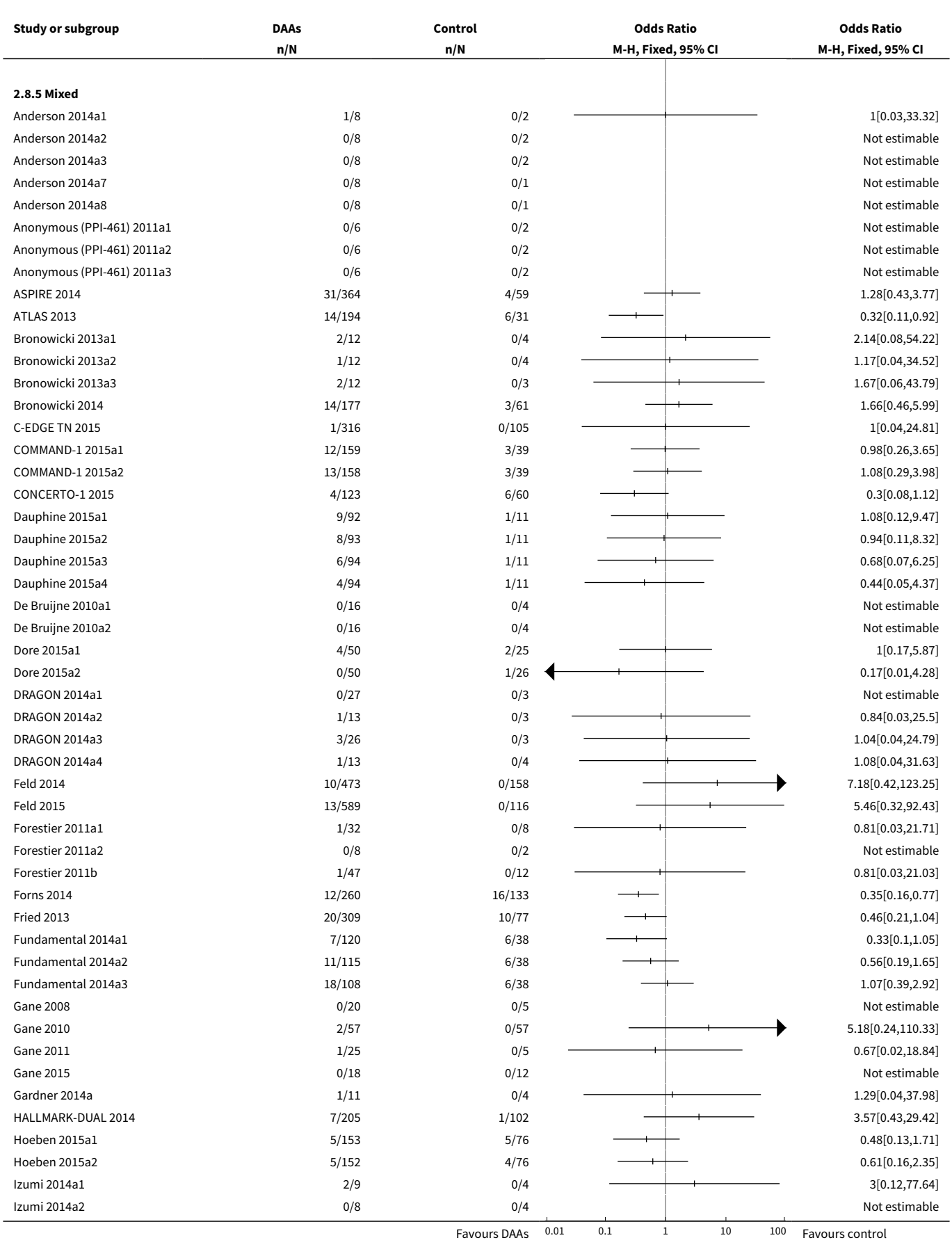
Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.7.2 Genotype 2				
2.7.3 Genotype 3				
2.7.4 Genotype 4				
2.7.5 Mixed				
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Gane 2008	0/20	0/5		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lawitz 2015	0/39	0/17		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]



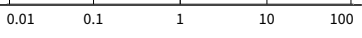
Analysis 2.8. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 8 Serious adverse events - according to human genotype (IL28b).

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.8.1 IL28b (CC)				
2.8.2 IL28B (CT)				
2.8.3 IL28B (TT)				
2.8.4 IL28B (CT + TT)				



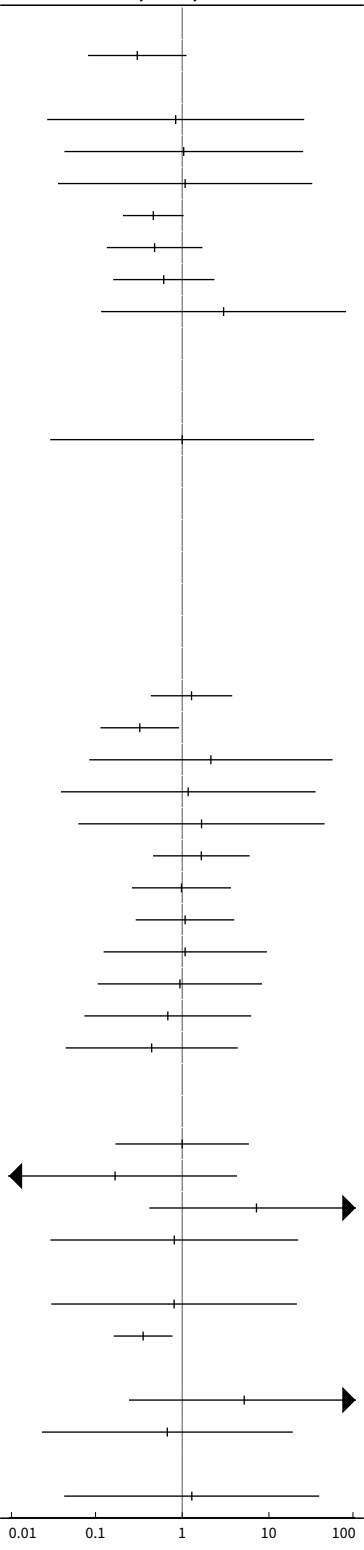
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.8.5 Mixed				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]



Analysis 2.9. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 9 Serious adverse events - according to Asian-region.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.9.1 From Asian region				
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
2.9.2 Not from Asian region				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.9.3 Mixed				
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]

Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
2.9.4 Unclear				
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Sullivan 2012	0/28	0/9		Not estimable

Favours DAAs 0.01 0.1 1 10 100 Favours control

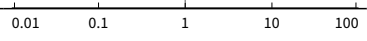
Analysis 2.10. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 10 Serious adverse events - according to specific ethnicities.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.10.1 White				
2.10.2 Black				
2.10.3 Hispanic				
2.10.4 Mixed				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]

Favours DAAs 0.01 0.1 1 10 100 Favours control

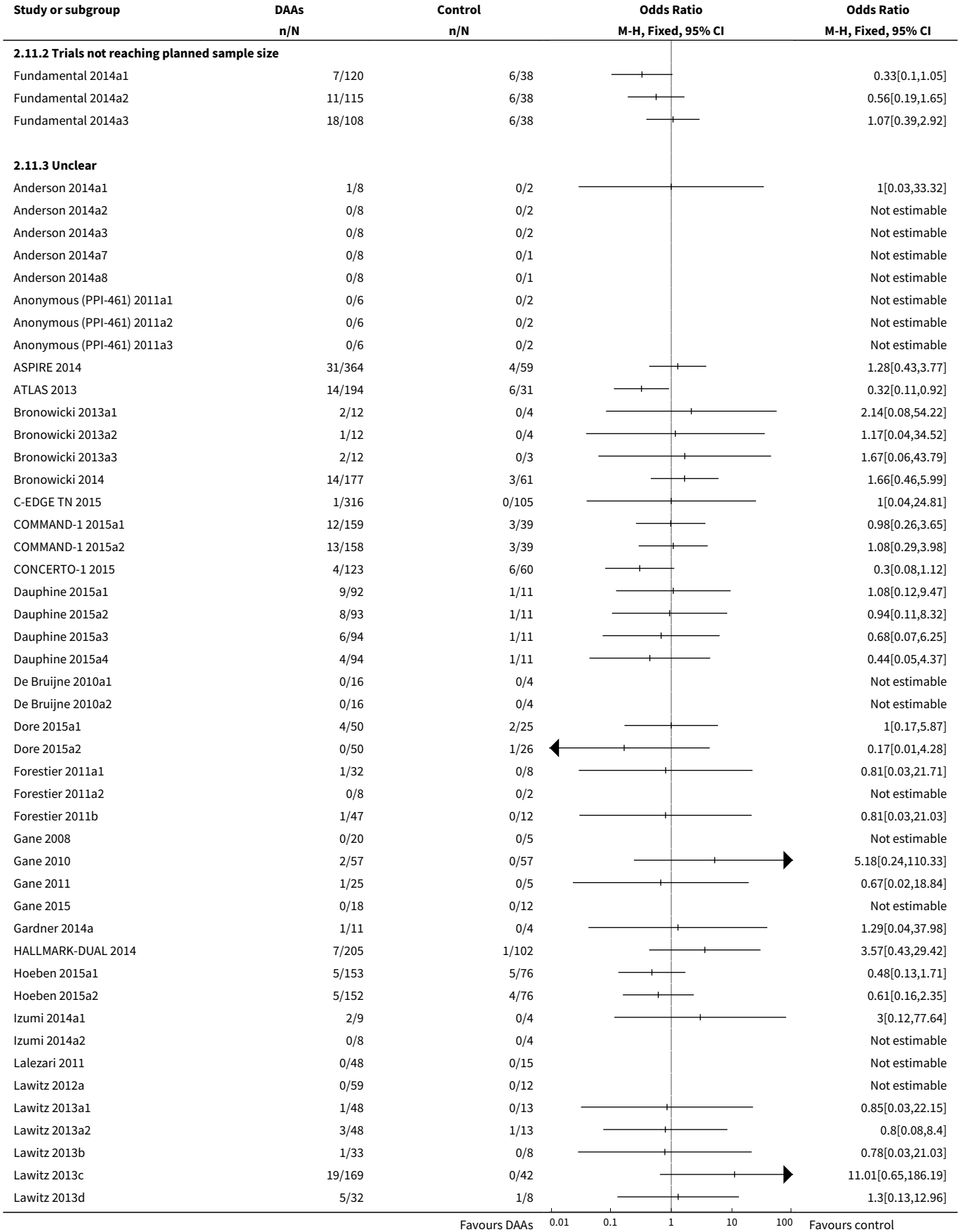
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.10.5 Unclear				



Analysis 2.11. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 11 Serious adverse events - according to reaching planned sample size.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.11.1 Trials reaching planned sample size				
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable

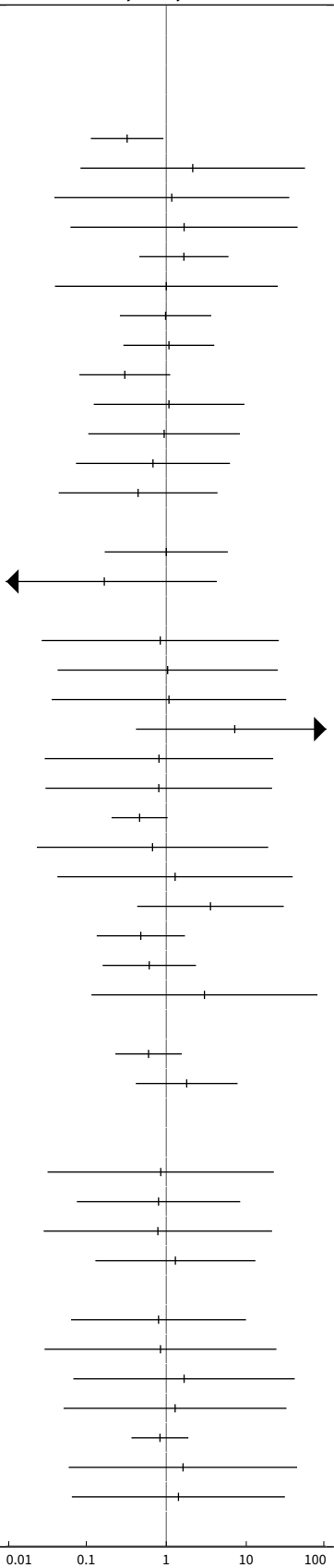
Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 2.12. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 12 Serious adverse events - according to prior treatment.

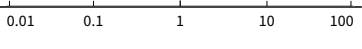
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.12.1 Treatment-naive				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable

Favours DAAs 0.01 0.1 1 10 100 Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2011a1	0/4	0/1		Not estimable



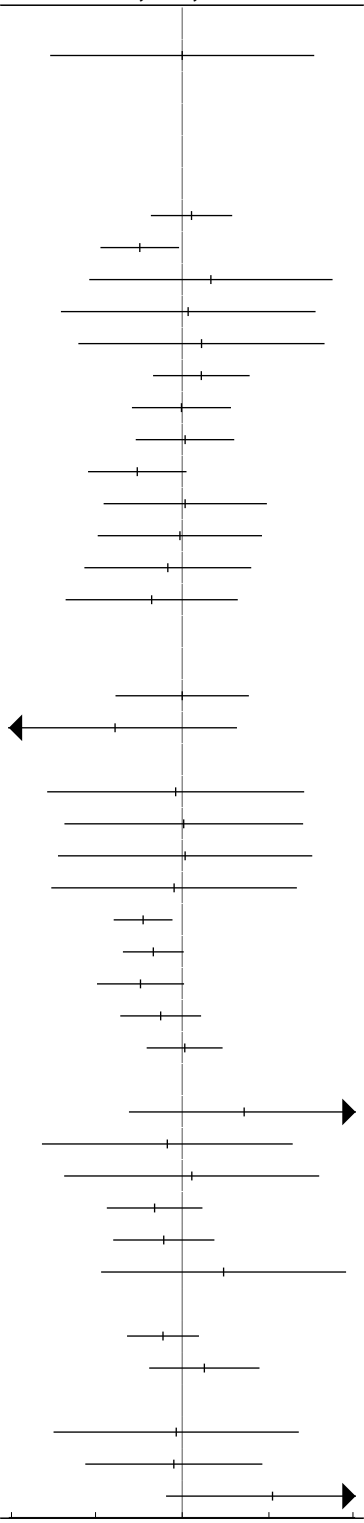
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.12.2 Treatment-experienced				
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
De Bruijne 2010a2	0/16	0/4		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
2.12.3 Mixed				
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Lawitz 2013e	0/35	0/5		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Sims 2014	0/20	0/4		Not estimable
Vince 2014	0/52	0/12		Not estimable
2.12.4 Unclear				
Gane 2015	0/18	0/12		Not estimable



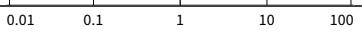
Favours DAAs Favours control

Analysis 2.13. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 13 Serious adverse events - according to interferon.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.13.1 Trials where both groups received interferon				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]



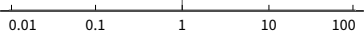
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
2.13.2 Trials where neither group received interferon				
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Reddy 2007	0/32	0/8		Not estimable
Sims 2014	0/20	0/4		Not estimable
Vince 2014	0/52	0/12		Not estimable



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.13.3 Unclear				
Gane 2015	0/18	0/12		Not estimable
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]

Analysis 2.14. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 14 Serious adverse events - according to ribavirin.

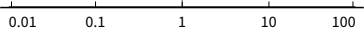
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.14.1 Trials where both groups received ribavirin				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
2.14.2 Trials where neither group received ribavirin				
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]

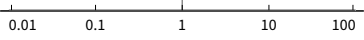
Favours DAAs | Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Reddy 2007	0/32	0/8		Not estimable
Sims 2014	0/20	0/4		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.14.3 Unclear				
Gane 2015	0/18	0/12		Not estimable



Analysis 2.15. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 15 Serious adverse events - according to chronic kidney disease.

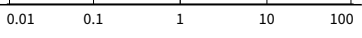
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.15.1 With chronic kidney disease				
2.15.2 Without chronic kidney disease				
2.15.3 Unclear				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]

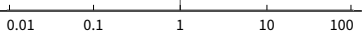
Favours DAAs Favours control

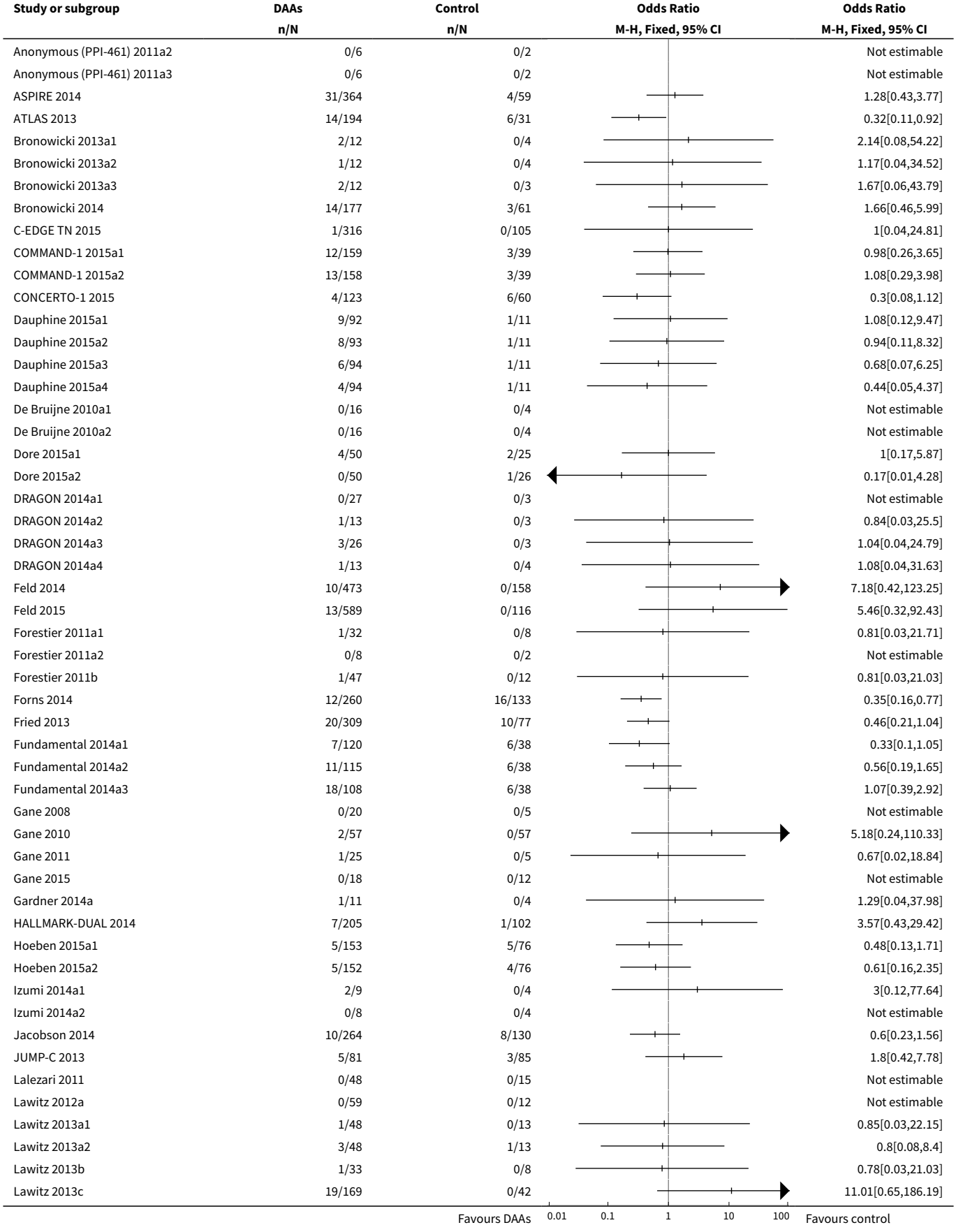
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]



Analysis 2.16. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 16 Serious adverse events - according to cryoglobulinaemia.

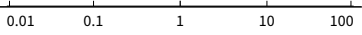
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.16.1 With cryoglobulinaemia				
2.16.2 Without cryoglobulinaemia				
2.16.3 Unclear				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable





Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]

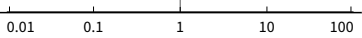
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]



Favours DAAs Favours control

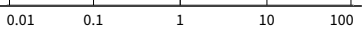
Analysis 2.17. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 17 Serious adverse events - according to DAA group as co-intervention.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.17.1 Trials where DAA were used as co-intervention				
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
2.17.2 Trials where DAA were not a co-intervention				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable



Favours DAAs | Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]

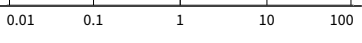
Favours DAAs 0.01 0.1 1 10 100 Favours control

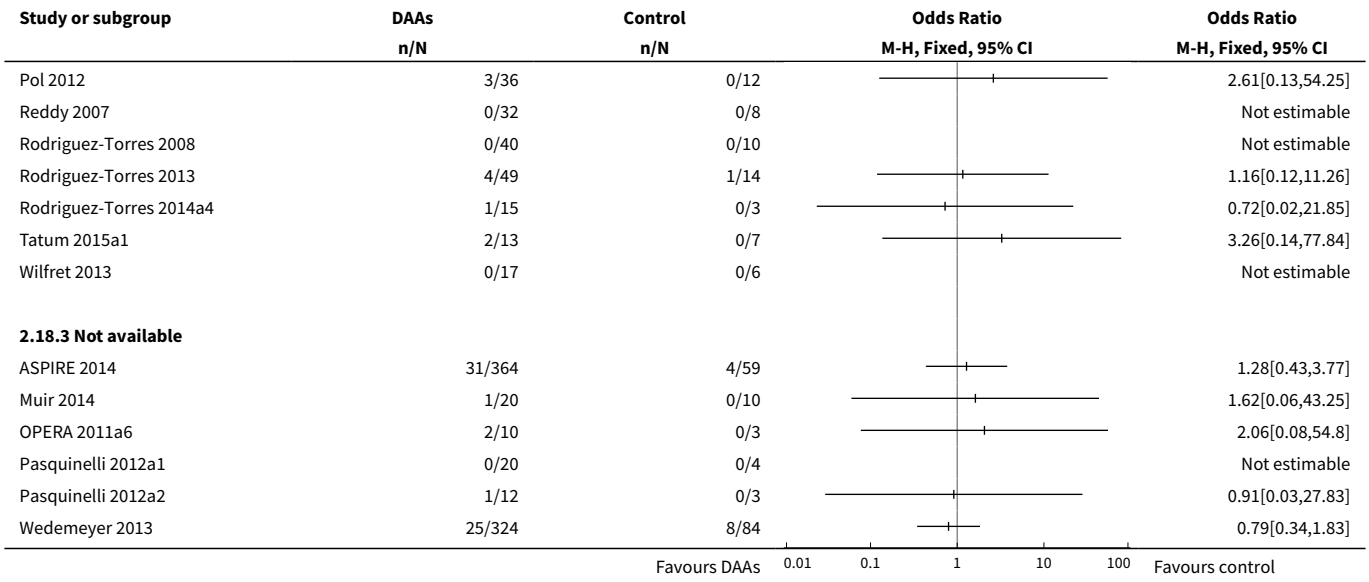
Analysis 2.18. Comparison 2 DAA on or on the way to the market versus placebo/no intervention (serious adverse events analyses), Outcome 18 Serious adverse events - according to median dose.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.18.1 Over or equal to median dose				
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2015	0/39	0/17		Not estimable

Favours DAAs 0.01 0.1 1 10 100 Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
2.18.2 Under median dose				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a7	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
De Bruijne 2010a2	0/16	0/4		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013e	0/35	0/5		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]





Comparison 3. DAA on or on the way to the market versus placebo/no intervention (sustained virological response)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Without sustained virological response	61	7115	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
2 Without sustained virological response - bias risk	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
2.1 Trials at high risk of bias	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
2.2 Trials at low risk of bias	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Without sustained virological response - according to type of DAA	61	7115	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
3.1 ABT-072	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 ACH-2684	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Alisporivir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 ALS-2200	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Asunaprevir	4	285	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.29, 0.85]
3.6 Balapiravir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 Beclabuvir	2	39	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.43, 1.40]
3.8 BILB-1941	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9 BIT-225	1	23	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.03, 2.51]
3.10 Boceprevir	1	229	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.29, 0.61]
3.11 Ciluprevir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.12 Daclatasvir	7	619	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.50, 0.73]
3.13 Danoprevir	5	642	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.28, 0.51]
3.14 Dasabuvir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.15 Deleobuvir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.16 Faldaprevir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.17 Filibuvir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.18 Grazoprevir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.19 GS-6620	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.20 GS-9256	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.21 GS-9451	1	329	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.26, 0.67]
3.22 GS-9669	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.23 GS-9851	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.24 GS-9857	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.25 GSK2336805	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.26 GSK2878175	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.27 IDX-184	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.28 INX-08189	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.29 Ledispasvir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.30 Mericitabine	4	725	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.49, 1.27]
3.31 Narlaprevir	2	40	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.43, 1.09]
3.32 Nesbuvir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.33 Odalasavir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.34 Ombitasvir	1	37	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.39, 1.07]
3.35 Paritaprevir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.36 PHX1766	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.37 PPI-461	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.38 PSI-352938	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.39 Samatasvir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.40 Setrobuvir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.41 Simeprevir	19	2898	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.33, 0.46]
3.42 Sofosbuvir	3	181	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.20, 0.58]
3.43 Sovaprevir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.44 Tegobuvir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.45 Telaprevir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.46 Valopicitabine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.47 Vaniprevir	9	333	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.25, 0.43]
3.48 VCH-759	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.49 VCH-916	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.50 Velpatasvir	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.51 VX-222	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.52 Mixed	2	735	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 7.05]
4 Without sustained virological response - according to group of DAA	61	7115	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
4.1 Cyclophilin	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 NS3/NS4A inhibitors	41	4756	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.36, 0.46]
4.3 NS5B inhibitors (NPI)	7	906	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.36, 0.90]
4.4 NS5B inhibitors (NNPI)	2	39	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.43, 1.40]
4.5 NS5A inhibitors	9	686	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.49, 0.69]
4.6 VPU-ion channel inhibitors	1	23	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.03, 2.51]
4.7 Mixed	1	705	Risk Ratio (M-H, Random, 95% CI)	0.01 [0.00, 0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Without sustained virological response - according to HIV-infection	61	7115	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
5.1 With HIV-infection	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Without HIV-infection	58	6726	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
5.3 Mixed (with and without HIV-infection)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.4 Unclear	3	389	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.35, 0.72]
6 Without sustained virological response - according to comorbidity	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
6.1 With comorbidity	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Without comorbidity	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
6.3 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Without sustained virological response - according to viral genotype	58	7098	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.36, 0.51]
7.1 Genotype 1	54	5984	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.37, 0.50]
7.2 Genotype 2	3	185	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 3.21]
7.3 Genotype 3	2	80	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.43, 1.43]
7.4 Genotype 4	5	226	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.02, 0.68]
7.5 Genotype 6	1	49	Risk Ratio (M-H, Random, 95% CI)	0.01 [0.00, 0.20]
7.6 Mixed	2	574	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.52, 1.62]
8 Without sustained virological response - according to human genotype (IL28b)	58	6745	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.40, 0.54]
8.1 IL28b (CC)	25	1444	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.29, 0.61]
8.2 IL28B (CT)	10	1304	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.42, 0.66]
8.3 IL28B (TT)	10	359	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.44, 0.67]
8.4 IL28B (CT + TT)	14	1798	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.57]
8.5 Unclear	7	147	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.33, 0.68]
8.6 Mixed	26	1693	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.40, 0.63]

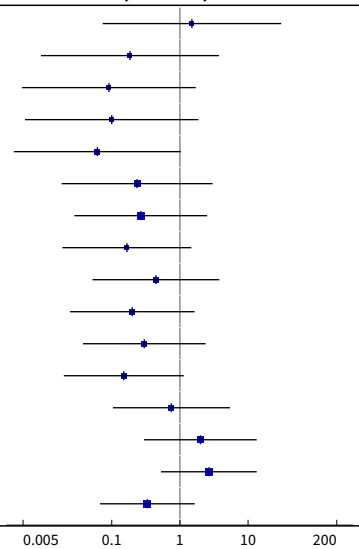
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Without sustained virological response - according to Asian-region	61	7115	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
9.1 From Asian region	10	1128	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.28, 0.42]
9.2 Not from Asian region	42	4910	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.43, 0.60]
9.3 Mixed	7	1010	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.03, 1.17]
9.4 Unclear	2	67	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.79]
10 Without sustained virological response - according to specific ethnicities	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
10.1 White	2	412	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.15, 0.38]
10.2 Black	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Hispanic	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 Mixed	48	5384	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.20, 0.27]
10.5 Unclear	9	862	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.20, 0.39]
10.6 Asian	2	457	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.23, 0.63]
11 Without sustained virological response - according to reaching planned sample size	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
11.1 Trials reaching planned sample size	13	3071	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.18, 0.25]
11.2 Trials not reaching planned sample size	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Unclear	48	4044	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.23, 0.33]
12 Without sustained virological response - according to prior treatment	61	7115	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
12.1 Treatment-naive	44	4777	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.41, 0.56]
12.2 Treatment-experienced	13	1274	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.36, 0.69]
12.3 Mixed	4	1064	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 0.96]
12.4 Unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Without sustained virological response - according to interferon	61	7115	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]

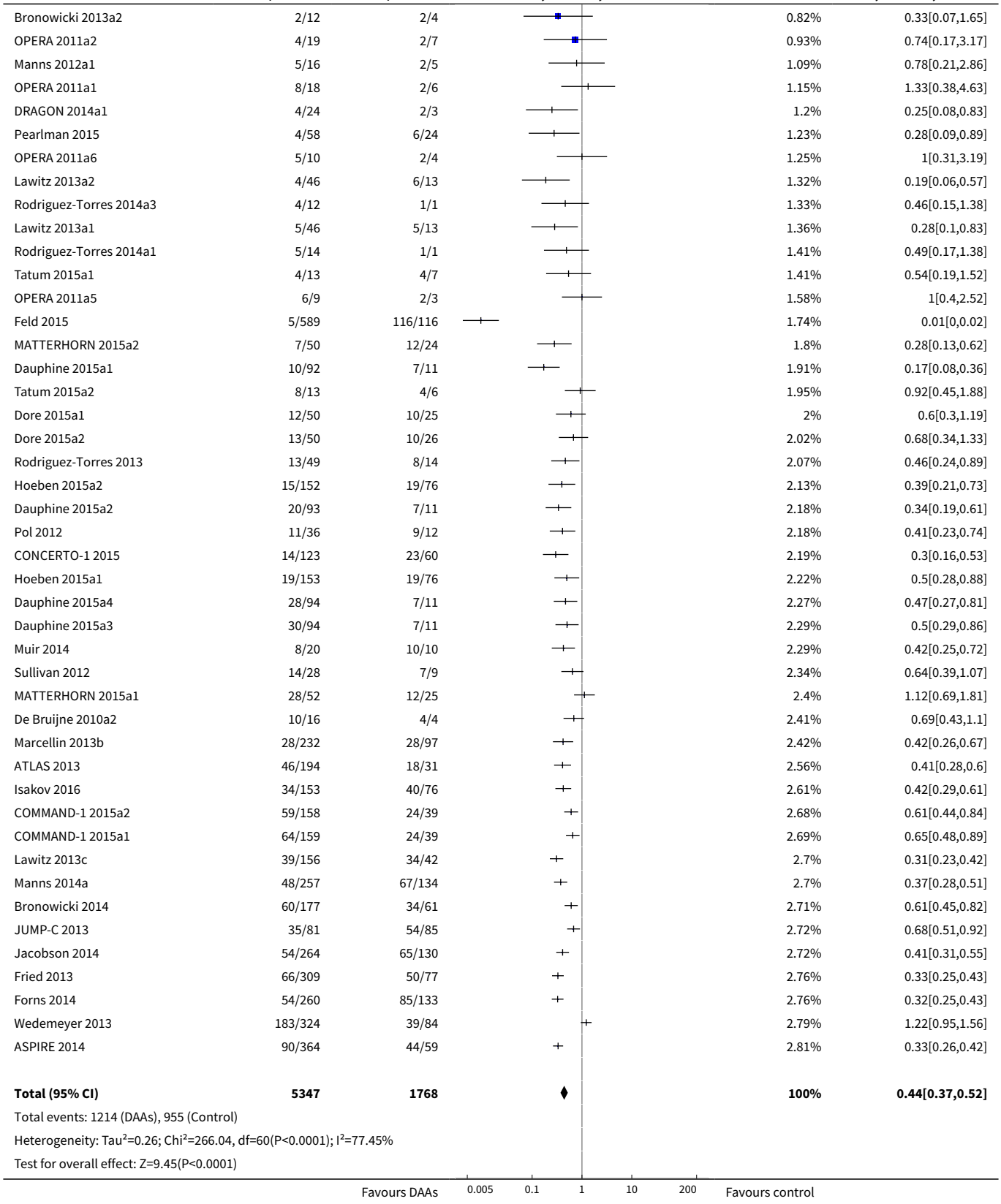
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Trials where both groups received interferon	57	6229	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.41, 0.54]
13.2 Trials where neither group received interferon	2	735	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 7.05]
13.3 Trials where only the experimental group received interferon	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.4 Trials where only the control group received interferon	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.5 Mixed	2	151	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.15, 2.30]
14 Without sustained virological response - according to ribavirin	61	7115	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
14.1 Trials where both groups received ribavirin	60	6410	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.41, 0.55]
14.2 Trials where neither group received ribavirin	1	705	Risk Ratio (M-H, Random, 95% CI)	0.01 [0.00, 0.02]
14.3 Trials where only the experimental group received ribavirin	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.4 Trials where only the control group received ribavirin	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Without sustained virological response - according to chronic kidney disease	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
15.1 With chronic kidney disease	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Without chronic kidney disease	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Unclear	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
16 Without sustained virological response - according to cryoglobulinaemia	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
16.1 With cryoglobulinaemia	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Without cryoglobulinaemia	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Unclear	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 Without sustained virological response - according to DAA group as co-intervention	61	7115	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.22, 0.27]
17.1 Trials where DAA were used as co-intervention	3	480	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.27, 0.66]
17.2 Trials where DAA were not a co-intervention	58	6635	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.21, 0.26]
18 Without sustained virological response - 'Best-worst case' scenario	61	7294	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.34, 0.49]
19 Without sustained virological response - 'Worst-best case' scenario	61	7294	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.43, 0.60]
20 Without sustained virological response - according to median dose	61	7115	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
20.1 Over or equal to median dose	34	4154	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.32, 0.53]
20.2 Under median dose	23	2086	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.39, 0.55]
20.3 Not available	4	875	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.26, 1.47]

Analysis 3.1. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 1 Without sustained virological response.

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Izumi 2014a1	1/9	0/4		0.29%	1.5[0.07,30.59]
Izumi 2014a2	0/8	1/4		0.29%	0.19[0.01,3.75]
Rodriguez-Torres 2014a4	0/10	1/2		0.3%	0.09[0,1.71]
Rodriguez-Torres 2014a2	0/9	1/2		0.3%	0.1[0.01,1.87]
Bronowicki 2013a3	0/12	2/3		0.32%	0.06[0,1.03]
Manns 2012a2	1/17	1/4		0.39%	0.24[0.02,3.01]
Tanwandee 2012	1/15	2/8		0.48%	0.27[0.03,2.51]
Manns 2012a3	1/15	2/5		0.51%	0.17[0.02,1.47]
Manns 2012a4	2/18	1/4		0.52%	0.44[0.05,3.79]
DRAGON 2014a4	1/10	2/4		0.54%	0.2[0.02,1.64]
DRAGON 2014a3	2/20	1/3		0.55%	0.3[0.04,2.38]
DRAGON 2014a2	1/10	2/3		0.57%	0.15[0.02,1.14]
De Bruijne 2010a1	3/16	1/4		0.59%	0.75[0.1,5.43]
OPERA 2011a3	6/18	1/6		0.63%	2[0.3,13.44]
OPERA 2011a4	8/9	1/3		0.81%	2.67[0.53,13.43]
Bronowicki 2013a1	2/12	2/4		0.82%	0.33[0.07,1.65]

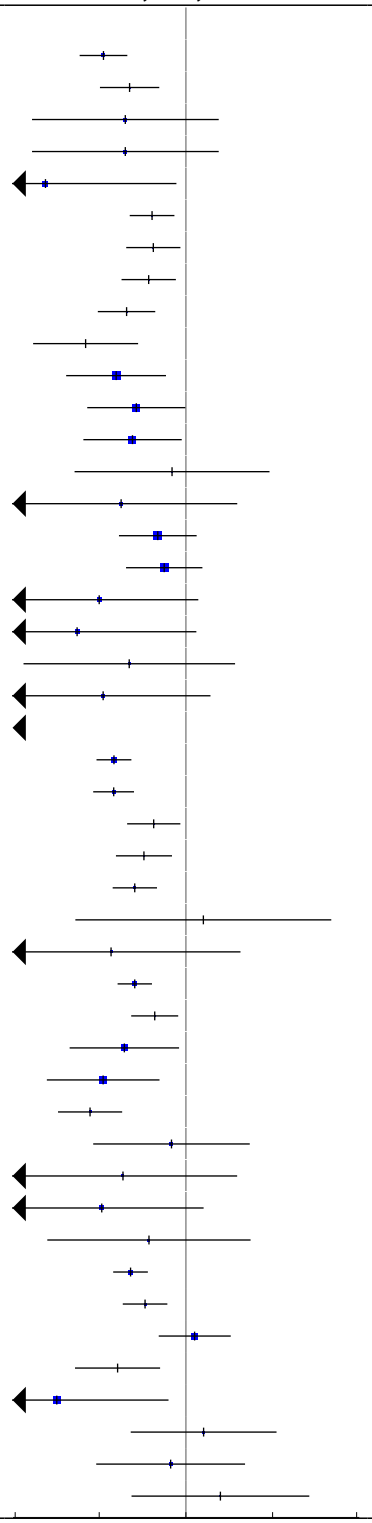




Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bronowicki 2013a2	2/12	2/4		0.82%	0.33[0.07,1.65]
OPERA 2011a2	4/19	2/7		0.93%	0.74[0.17,3.17]
Manns 2012a1	5/16	2/5		1.09%	0.78[0.21,2.86]
OPERA 2011a1	8/18	2/6		1.15%	1.33[0.38,4.63]
DRAGON 2014a1	4/24	2/3		1.2%	0.25[0.08,0.83]
Pearlman 2015	4/58	6/24		1.23%	0.28[0.09,0.89]
OPERA 2011a6	5/10	2/4		1.25%	1[0.31,3.19]
Lawitz 2013a2	4/46	6/13		1.32%	0.19[0.06,0.57]
Rodriguez-Torres 2014a3	4/12	1/1		1.33%	0.46[0.15,1.38]
Lawitz 2013a1	5/46	5/13		1.36%	0.28[0.1,0.83]
Rodriguez-Torres 2014a1	5/14	1/1		1.41%	0.49[0.17,1.38]
Tatum 2015a1	4/13	4/7		1.41%	0.54[0.19,1.52]
OPERA 2011a5	6/9	2/3		1.58%	1[0.4,2.52]
Feld 2015	5/589	116/116		1.74%	0.01[0,0.02]
MATTERHORN 2015a2	7/50	12/24		1.8%	0.28[0.13,0.62]
Dauphine 2015a1	10/92	7/11		1.91%	0.17[0.08,0.36]
Tatum 2015a2	8/13	4/6		1.95%	0.92[0.45,1.88]
Dore 2015a1	12/50	10/25		2%	0.6[0.3,1.19]
Dore 2015a2	13/50	10/26		2.02%	0.68[0.34,1.33]
Rodriguez-Torres 2013	13/49	8/14		2.07%	0.46[0.24,0.89]
Hoeben 2015a2	15/152	19/76		2.13%	0.39[0.21,0.73]
Dauphine 2015a2	20/93	7/11		2.18%	0.34[0.19,0.61]
Pol 2012	11/36	9/12		2.18%	0.41[0.23,0.74]
CONCERTO-1 2015	14/123	23/60		2.19%	0.3[0.16,0.53]
Hoeben 2015a1	19/153	19/76		2.22%	0.5[0.28,0.88]
Dauphine 2015a4	28/94	7/11		2.27%	0.47[0.27,0.81]
Dauphine 2015a3	30/94	7/11		2.29%	0.5[0.29,0.86]
Muir 2014	8/20	10/10		2.29%	0.42[0.25,0.72]
Sullivan 2012	14/28	7/9		2.34%	0.64[0.39,1.07]
MATTERHORN 2015a1	28/52	12/25		2.4%	1.12[0.69,1.81]
De Bruijne 2010a2	10/16	4/4		2.41%	0.69[0.43,1.1]
Marcellin 2013b	28/232	28/97		2.42%	0.42[0.26,0.67]
ATLAS 2013	46/194	18/31		2.56%	0.41[0.28,0.6]
Isakov 2016	34/153	40/76		2.61%	0.42[0.29,0.61]
COMMAND-1 2015a2	59/158	24/39		2.68%	0.61[0.44,0.84]
COMMAND-1 2015a1	64/159	24/39		2.69%	0.65[0.48,0.89]
Lawitz 2013c	39/156	34/42		2.7%	0.31[0.23,0.42]
Manns 2014a	48/257	67/134		2.7%	0.37[0.28,0.51]
Bronowicki 2014	60/177	34/61		2.71%	0.61[0.45,0.82]
JUMP-C 2013	35/81	54/85		2.72%	0.68[0.51,0.92]
Jacobson 2014	54/264	65/130		2.72%	0.41[0.31,0.55]
Fried 2013	66/309	50/77		2.76%	0.33[0.25,0.43]
Forns 2014	54/260	85/133		2.76%	0.32[0.25,0.43]
Wedemeyer 2013	183/324	39/84		2.79%	1.22[0.95,1.56]
ASPIRE 2014	90/364	44/59		2.81%	0.33[0.26,0.42]
Total (95% CI)	**5347**	**1768**		**100%**	**0.44[0.37,0.52]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau^2=0.26; Chi^2=266.04, df=60(P<0.0001); I^2=77.45%					
Test for overall effect: Z=9.45(P<0.0001)					

Analysis 3.2. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 2 Without sustained virological response - bias risk.

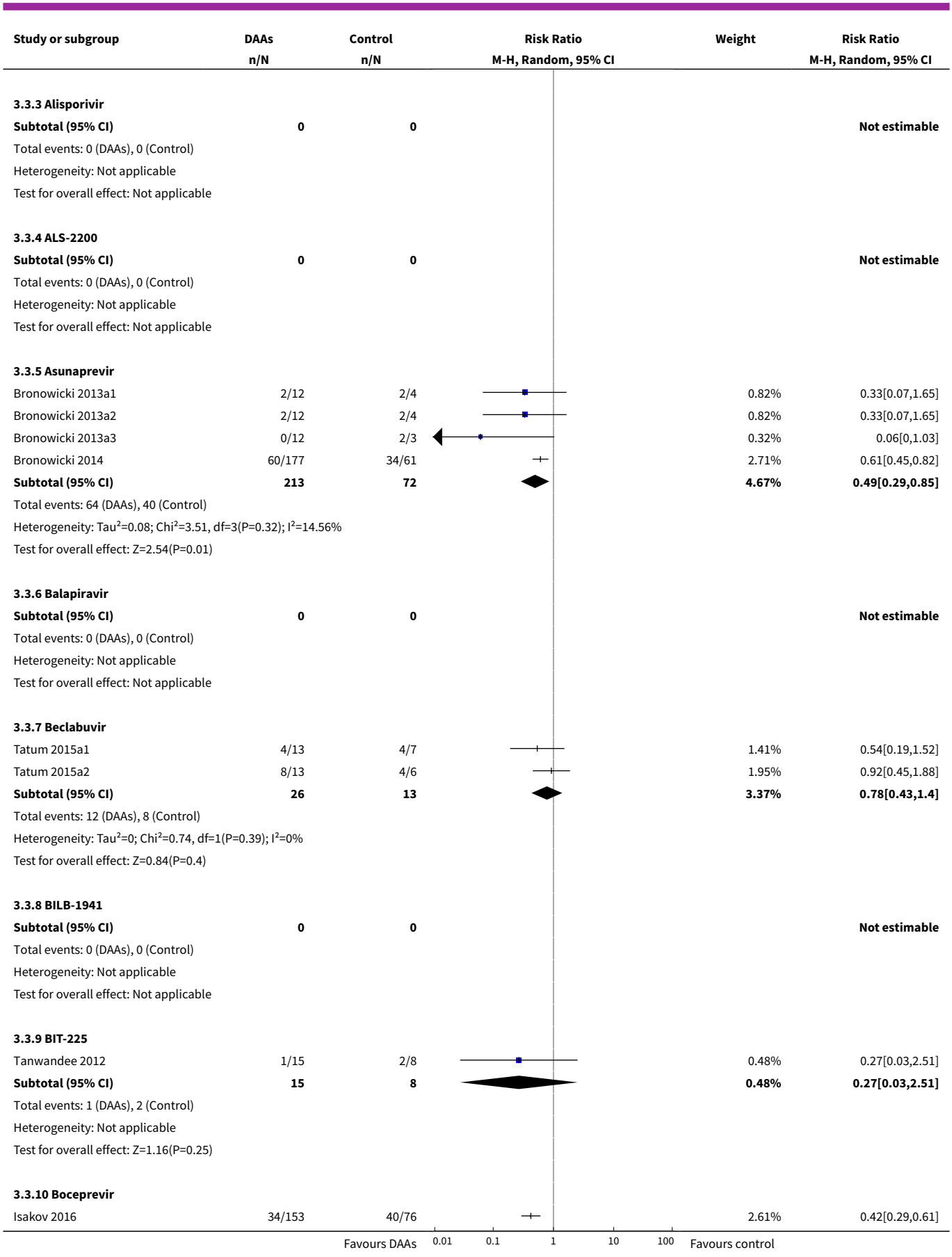
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.2.1 Trials at high risk of bias					
ASPIRE 2014	90/364	44/59		5.26%	0.11[0.06,0.21]
ATLAS 2013	46/194	18/31		2.18%	0.22[0.1,0.49]
Bronowicki 2013a1	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a2	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a3	0/12	2/3		0.34%	0.02[0,0.78]
Bronowicki 2014	60/177	34/61		3.08%	0.41[0.22,0.74]
COMMAND-1 2015a1	64/159	24/39		2.12%	0.42[0.21,0.86]
COMMAND-1 2015a2	59/158	24/39		2.23%	0.37[0.18,0.77]
CONCERTO-1 2015	14/123	23/60		2.53%	0.21[0.1,0.44]
Dauphine 2015a1	10/92	7/11		1.03%	0.07[0.02,0.28]
Dauphine 2015a2	20/93	7/11		0.91%	0.16[0.04,0.59]
Dauphine 2015a3	30/94	7/11		0.79%	0.27[0.07,0.99]
Dauphine 2015a4	28/94	7/11		0.81%	0.24[0.07,0.89]
De Bruijne 2010a1	3/16	1/4		0.12%	0.69[0.05,9.21]
De Bruijne 2010a2	10/16	4/4		0.25%	0.18[0.01,3.91]
Dore 2015a1	12/50	10/25		0.93%	0.47[0.17,1.33]
Dore 2015a2	13/50	10/26		0.9%	0.56[0.2,1.55]
DRAGON 2014a1	4/24	2/3		0.27%	0.1[0.01,1.39]
DRAGON 2014a2	1/10	2/3		0.26%	0.06[0,1.32]
DRAGON 2014a3	2/20	1/3		0.14%	0.22[0.01,3.69]
DRAGON 2014a4	1/10	2/4		0.24%	0.11[0.01,1.92]
Feld 2015	5/589	116/116		17.77%	0[0,0]
Forns 2014	54/260	85/133		8.22%	0.15[0.09,0.24]
Fried 2013	66/309	50/77		5.81%	0.15[0.09,0.25]
Hoeben 2015a1	19/153	19/76		2.05%	0.43[0.21,0.86]
Hoeben 2015a2	15/152	19/76		2.11%	0.33[0.16,0.69]
Isakov 2016	34/153	40/76		3.84%	0.26[0.14,0.46]
Izumi 2014a1	1/9	0/4		0.05%	1.59[0.05,47.52]
Izumi 2014a2	0/8	1/4		0.17%	0.14[0,4.26]
Jacobson 2014	54/264	65/130		6.39%	0.26[0.16,0.41]
JUMP-C 2013	35/81	54/85		2.76%	0.44[0.23,0.81]
Lawitz 2013a1	5/46	5/13		0.64%	0.2[0.05,0.83]
Lawitz 2013a2	4/46	6/13		0.79%	0.11[0.02,0.5]
Lawitz 2013c	39/156	34/42		3.71%	0.08[0.03,0.18]
Manns 2012a1	5/16	2/5		0.19%	0.68[0.09,5.45]
Manns 2012a2	1/17	1/4		0.14%	0.19[0.01,3.9]
Manns 2012a3	1/15	2/5		0.26%	0.11[0.01,1.6]
Manns 2012a4	2/18	1/4		0.13%	0.38[0.03,5.57]
Manns 2014a	48/257	67/134		6.61%	0.23[0.14,0.36]
Marcellin 2013b	28/232	28/97		3.2%	0.34[0.19,0.61]
MATTERHORN 2015a1	28/52	12/25		0.69%	1.26[0.49,3.29]
MATTERHORN 2015a2	7/50	12/24		1.29%	0.16[0.05,0.5]
Muir 2014	8/20	10/10		0.76%	0.03[0,0.63]
OPERA 2011a1	8/18	2/6		0.15%	1.6[0.23,11.08]
OPERA 2011a2	4/19	2/7		0.21%	0.67[0.09,4.81]
OPERA 2011a3	6/18	1/6		0.09%	2.5[0.24,26.48]

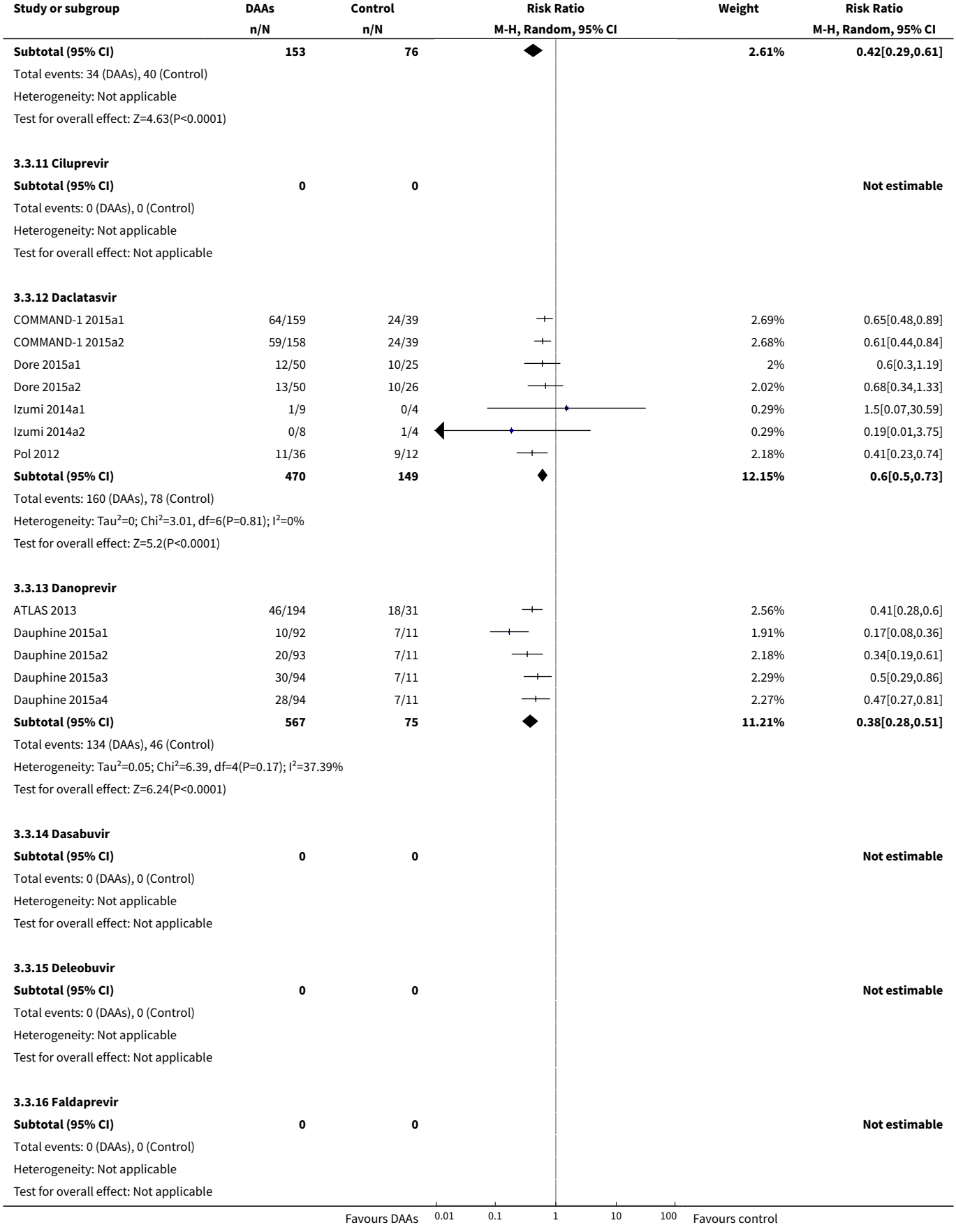


Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
OPERA 2011a4	8/9	1/3		0.02%	16[0.67,383.02]
OPERA 2011a5	6/9	2/3		0.09%	1[0.06,15.99]
OPERA 2011a6	5/10	2/4		0.13%	1[0.1,10.17]
Pearlman 2015	4/58	6/24		0.73%	0.22[0.06,0.88]
Pol 2012	11/36	9/12		0.86%	0.15[0.03,0.65]
Rodriguez-Torres 2013	13/49	8/14		0.84%	0.27[0.08,0.93]
Rodriguez-Torres 2014a1	5/14	1/1		0.15%	0.19[0.01,5.6]
Rodriguez-Torres 2014a2	0/9	1/2		0.2%	0.05[0,1.99]
Rodriguez-Torres 2014a3	4/12	1/1		0.16%	0.18[0.01,5.28]
Rodriguez-Torres 2014a4	0/10	1/2		0.21%	0.05[0,1.79]
Sullivan 2012	14/28	7/9		0.49%	0.29[0.05,1.62]
Tanwandee 2012	1/15	2/8		0.22%	0.21[0.02,2.84]
Tatum 2015a1	4/13	4/7		0.33%	0.33[0.05,2.24]
Tatum 2015a2	8/13	4/6		0.19%	0.8[0.1,6.1]
Wedemeyer 2013	183/324	39/84		2.49%	1.5[0.93,2.42]
Subtotal (95% CI)	**5347**	**1768**		**100%**	**0.24[0.22,0.27]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau^2=0; Chi^2=174.15, df=60(P<0.0001); I^2=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
3.2.2 Trials at low risk of bias					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**5347**	**1768**		**100%**	**0.24[0.22,0.27]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau^2=0; Chi^2=174.15, df=60(P<0.0001); I^2=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
Test for subgroup differences: Not applicable					

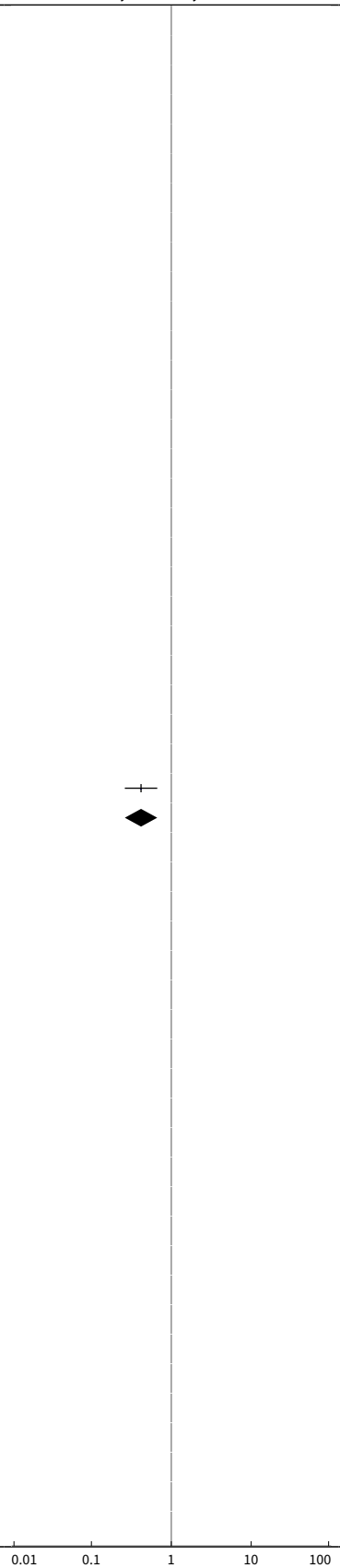
Analysis 3.3. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 3 Without sustained virological response - according to type of DAA.

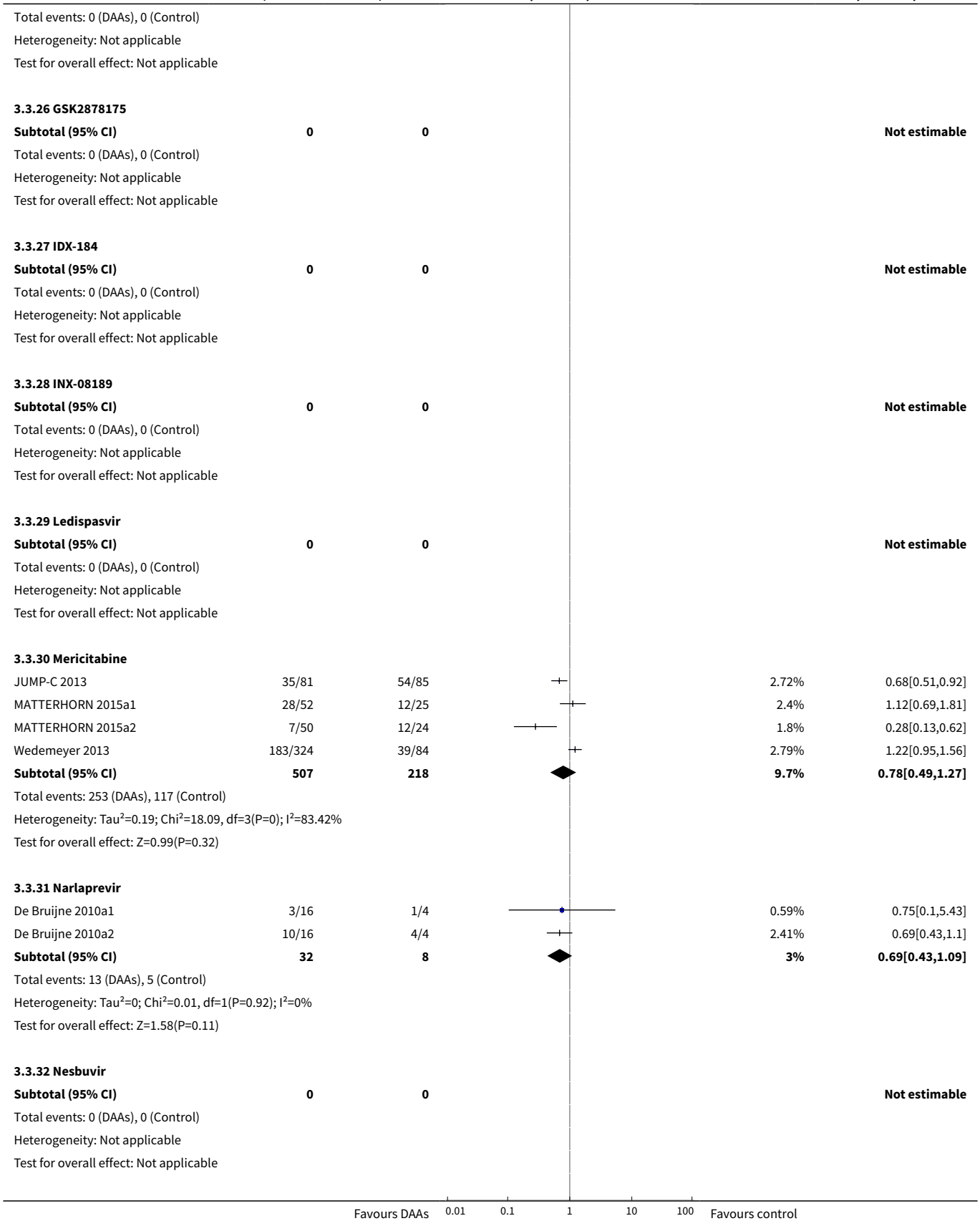
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 ABT-072					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.2 ACH-2684					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



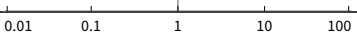


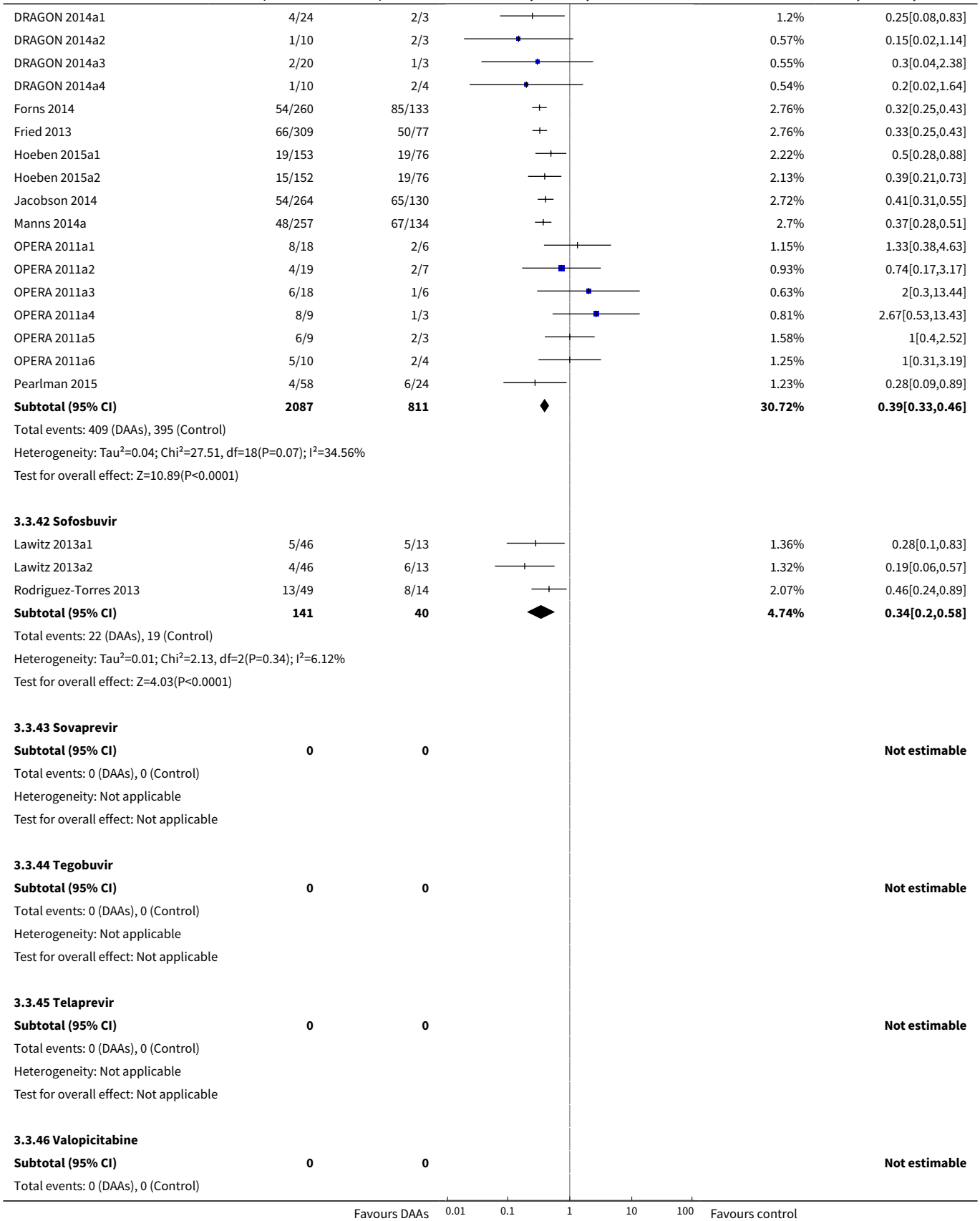
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.17 Filibuvir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.18 Grazoprevir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.19 GS-6620					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.20 GS-9256					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.21 GS-9451					
Marcellin 2013b	28/232	28/97		2.42%	0.42[0.26,0.67]
Subtotal (95% CI)	**232**	**97**		**2.42%**	**0.42[0.26,0.67]**
Total events: 28 (DAAs), 28 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.66(P=0)					
3.3.22 GS-9669					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.23 GS-9851					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.24 GS-9857					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.25 GSK2336805					
Subtotal (95% CI)	**0**	**0**			**Not estimable**





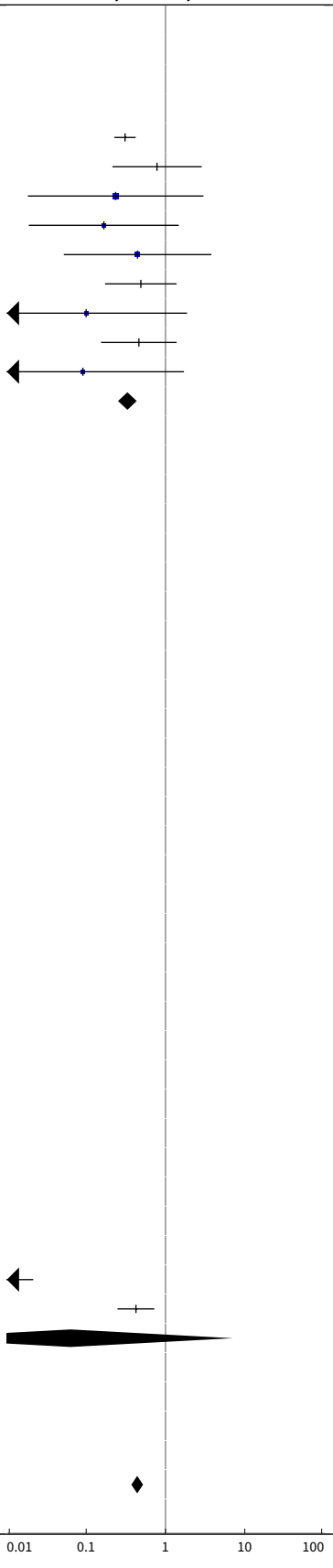
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.33 Odalasavir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.34 Ombitasvir					
Sullivan 2012	14/28	7/9		2.34%	0.64[0.39,1.07]
Subtotal (95% CI)	**28**	**9**		**2.34%**	**0.64[0.39,1.07]**
Total events: 14 (DAAs), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					
3.3.35 Paritaprevir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.36 PHX1766					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.37 PPI-461					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.38 PSI-352938					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.39 Samatasvir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.40 Setrobuvir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.41 Simeprevir					
ASPIRE 2014	90/364	44/59		2.81%	0.33[0.26,0.42]
CONCERTO-1 2015	14/123	23/60		2.19%	0.3[0.16,0.53]



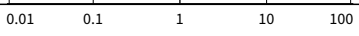


Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DRAGON 2014a1	4/24	2/3		1.2%	0.25[0.08,0.83]
DRAGON 2014a2	1/10	2/3		0.57%	0.15[0.02,1.14]
DRAGON 2014a3	2/20	1/3		0.55%	0.3[0.04,2.38]
DRAGON 2014a4	1/10	2/4		0.54%	0.2[0.02,1.64]
Forns 2014	54/260	85/133		2.76%	0.32[0.25,0.43]
Fried 2013	66/309	50/77		2.76%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.22%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		2.13%	0.39[0.21,0.73]
Jacobson 2014	54/264	65/130		2.72%	0.41[0.31,0.55]
Manns 2014a	48/257	67/134		2.7%	0.37[0.28,0.51]
OPERA 2011a1	8/18	2/6		1.15%	1.33[0.38,4.63]
OPERA 2011a2	4/19	2/7		0.93%	0.74[0.17,3.17]
OPERA 2011a3	6/18	1/6		0.63%	2[0.3,13.44]
OPERA 2011a4	8/9	1/3		0.81%	2.67[0.53,13.43]
OPERA 2011a5	6/9	2/3		1.58%	1[0.4,2.52]
OPERA 2011a6	5/10	2/4		1.25%	1[0.31,3.19]
Pearlman 2015	4/58	6/24		1.23%	0.28[0.09,0.89]
Subtotal (95% CI)	**2087**	**811**		**30.72%**	**0.39[0.33,0.46]**
Total events: 409 (DAAs), 395 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=27.51, df=18(P=0.07); I^2=34.56%					
Test for overall effect: Z=10.89(P<0.0001)					
3.3.42 Sofosbuvir					
Lawitz 2013a1	5/46	5/13		1.36%	0.28[0.1,0.83]
Lawitz 2013a2	4/46	6/13		1.32%	0.19[0.06,0.57]
Rodriguez-Torres 2013	13/49	8/14		2.07%	0.46[0.24,0.89]
Subtotal (95% CI)	**141**	**40**		**4.74%**	**0.34[0.2,0.58]**
Total events: 22 (DAAs), 19 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=2.13, df=2(P=0.34); I^2=6.12%					
Test for overall effect: Z=4.03(P<0.0001)					
3.3.43 Sovaprevir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.44 Tegobuvir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.45 Telaprevir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.46 Valopicitabine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.47 Vaniprevir					
Lawitz 2013c	39/156	34/42		2.7%	0.31[0.23,0.42]
Manns 2012a1	5/16	2/5		1.09%	0.78[0.21,2.86]
Manns 2012a2	1/17	1/4		0.39%	0.24[0.02,3.01]
Manns 2012a3	1/15	2/5		0.51%	0.17[0.02,1.47]
Manns 2012a4	2/18	1/4		0.52%	0.44[0.05,3.79]
Rodriguez-Torres 2014a1	5/14	1/1		1.41%	0.49[0.17,1.38]
Rodriguez-Torres 2014a2	0/9	1/2		0.3%	0.1[0.01,1.87]
Rodriguez-Torres 2014a3	4/12	1/1		1.33%	0.46[0.15,1.38]
Rodriguez-Torres 2014a4	0/10	1/2		0.3%	0.09[0,1.71]
Subtotal (95% CI)	**267**	**66**		**8.55%**	**0.33[0.25,0.43]**
Total events: 57 (DAAs), 44 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.72, df=8(P=0.79); I^2=0%					
Test for overall effect: Z=8.01(P<0.0001)					
3.3.48 VCH-759					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.49 VCH-916					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.50 Velpatasvir					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.51 VX-222					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.3.52 Mixed					
Feld 2015	5/589	116/116		1.74%	0.01[0,0.02]
Muir 2014	8/20	10/10		2.29%	0.42[0.25,0.72]
Subtotal (95% CI)	**609**	**126**		**4.03%**	**0.06[0,7.05]**
Total events: 13 (DAAs), 126 (Control)					
Heterogeneity: Tau^2=11.42; Chi^2=90.74, df=1(P<0.0001); I^2=98.9%					
Test for overall effect: Z=1.15(P=0.25)					
Total (95% CI)	**5347**	**1768**		**100%**	**0.44[0.37,0.52]**
Total events: 1214 (DAAs), 955 (Control)					

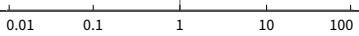


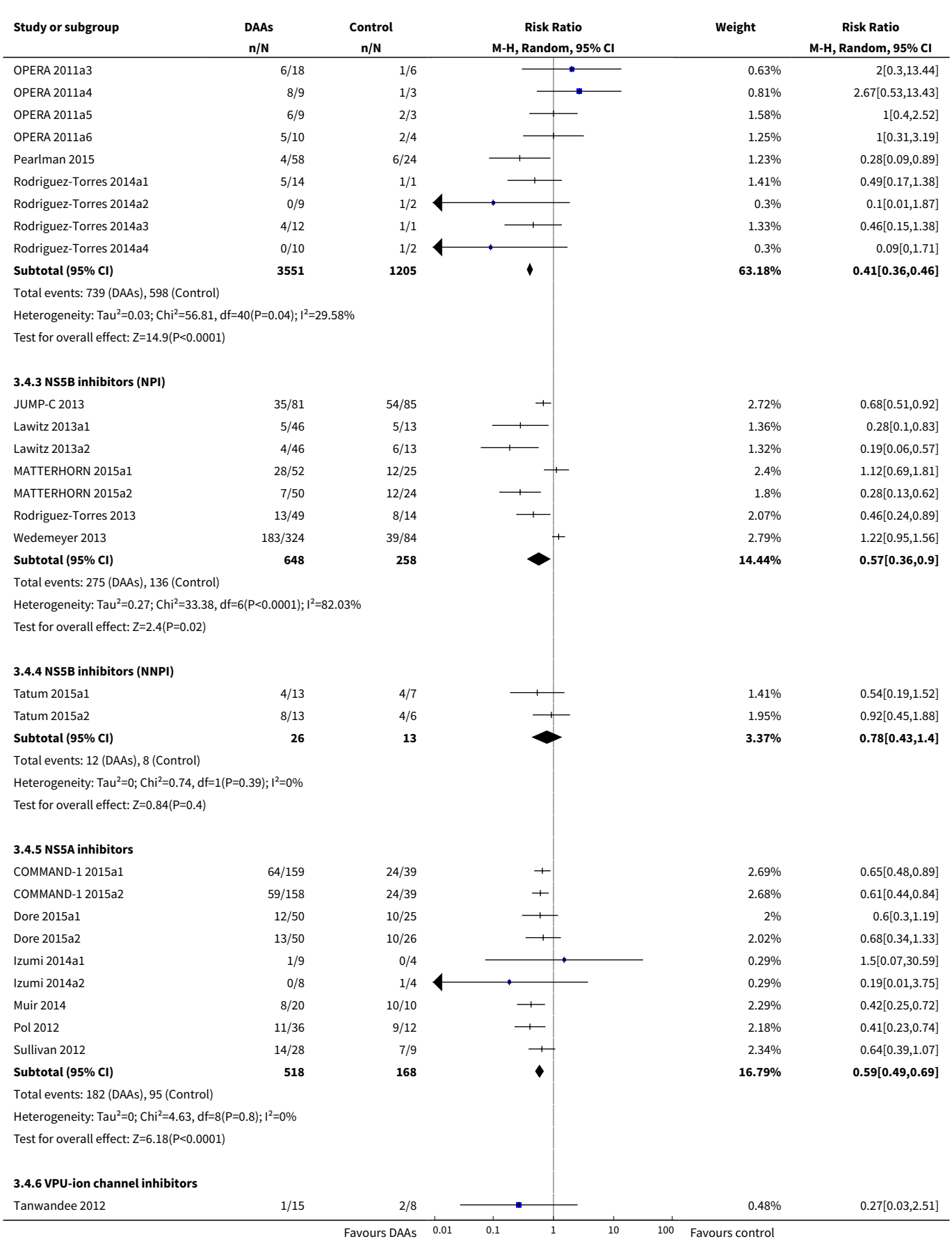
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.26; Chi²=266.04, df=60(P<0.0001); I²=77.45%					
Test for overall effect: Z=9.45(P<0.0001)					
Test for subgroup differences: Chi²=33.38, df=1 (P=0), I²=61.05%					

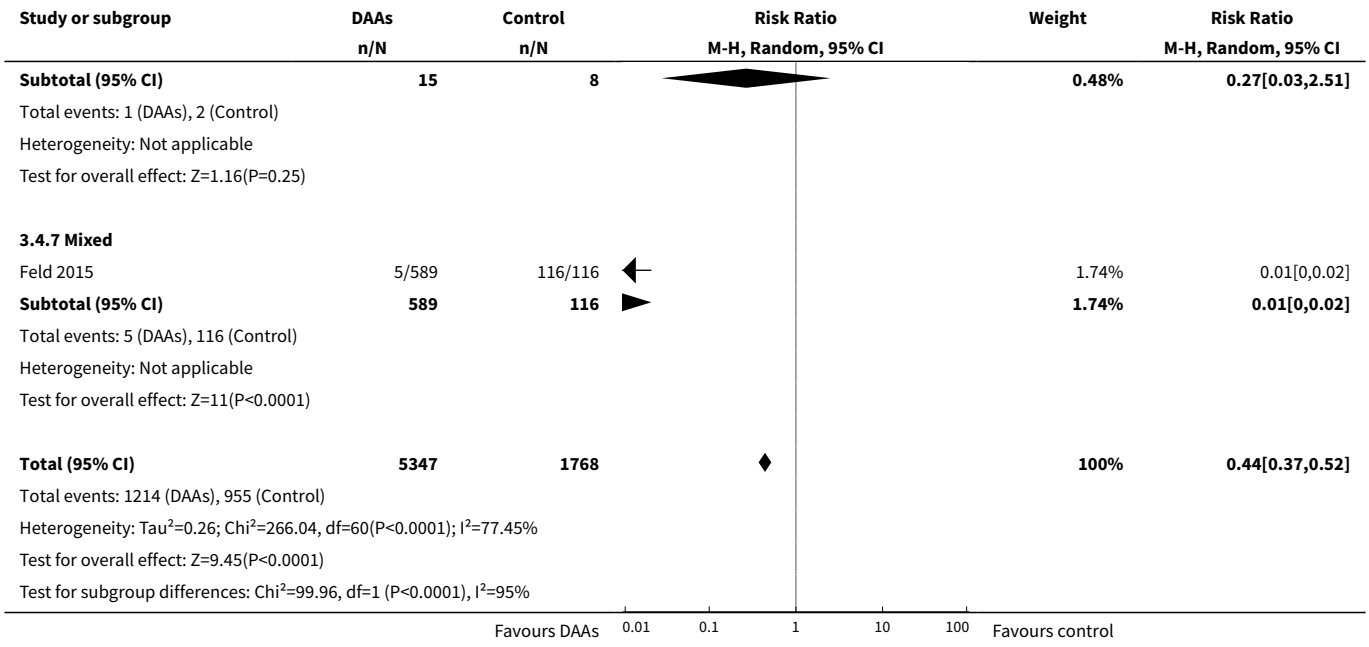


Analysis 3.4. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 4 Without sustained virological response - according to group of DAA.

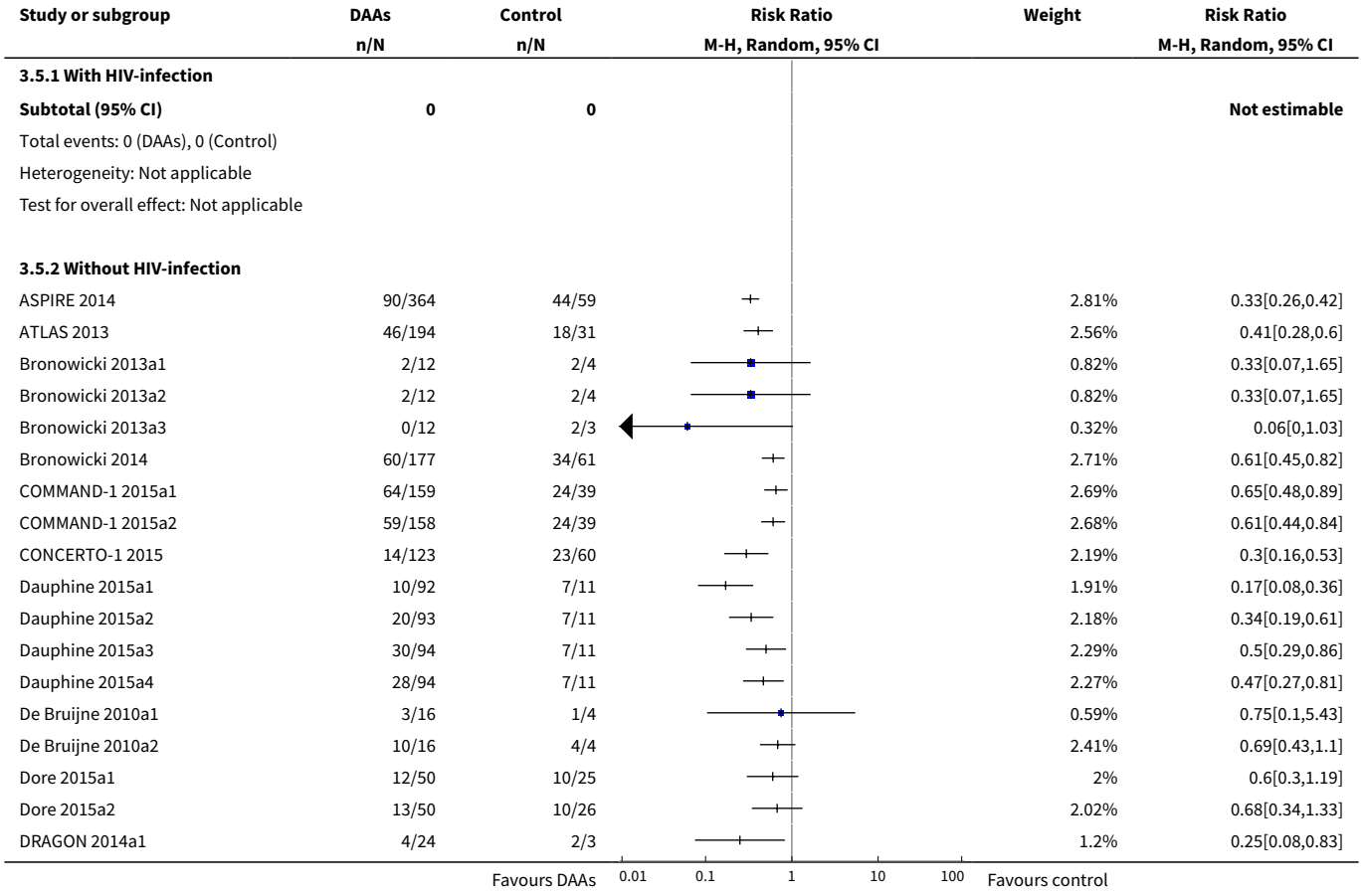
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Cyclophilin					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.4.2 NS3/NS4A inhibitors					
ASPIRE 2014	90/364	44/59		2.81%	0.33[0.26,0.42]
ATLAS 2013	46/194	18/31		2.56%	0.41[0.28,0.6]
Bronowicki 2013a1	2/12	2/4		0.82%	0.33[0.07,1.65]
Bronowicki 2013a2	2/12	2/4		0.82%	0.33[0.07,1.65]
Bronowicki 2013a3	0/12	2/3		0.32%	0.06[0,1.03]
Bronowicki 2014	60/177	34/61		2.71%	0.61[0.45,0.82]
CONCERTO-1 2015	14/123	23/60		2.19%	0.3[0.16,0.53]
Dauphine 2015a1	10/92	7/11		1.91%	0.17[0.08,0.36]
Dauphine 2015a2	20/93	7/11		2.18%	0.34[0.19,0.61]
Dauphine 2015a3	30/94	7/11		2.29%	0.5[0.29,0.86]
Dauphine 2015a4	28/94	7/11		2.27%	0.47[0.27,0.81]
De Bruijne 2010a1	3/16	1/4		0.59%	0.75[0.1,5.43]
De Bruijne 2010a2	10/16	4/4		2.41%	0.69[0.43,1.1]
DRAGON 2014a1	4/24	2/3		1.2%	0.25[0.08,0.83]
DRAGON 2014a2	1/10	2/3		0.57%	0.15[0.02,1.14]
DRAGON 2014a3	2/20	1/3		0.55%	0.3[0.04,2.38]
DRAGON 2014a4	1/10	2/4		0.54%	0.2[0.02,1.64]
Forns 2014	54/260	85/133		2.76%	0.32[0.25,0.43]
Fried 2013	66/309	50/77		2.76%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.22%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		2.13%	0.39[0.21,0.73]
Isakov 2016	34/153	40/76		2.61%	0.42[0.29,0.61]
Jacobson 2014	54/264	65/130		2.72%	0.41[0.31,0.55]
Lawitz 2013c	39/156	34/42		2.7%	0.31[0.23,0.42]
Manns 2012a1	5/16	2/5		1.09%	0.78[0.21,2.86]
Manns 2012a2	1/17	1/4		0.39%	0.24[0.02,3.01]
Manns 2012a3	1/15	2/5		0.51%	0.17[0.02,1.47]
Manns 2012a4	2/18	1/4		0.52%	0.44[0.05,3.79]
Manns 2014a	48/257	67/134		2.7%	0.37[0.28,0.51]
Marcellin 2013b	28/232	28/97		2.42%	0.42[0.26,0.67]
OPERA 2011a1	8/18	2/6		1.15%	1.33[0.38,4.63]
OPERA 2011a2	4/19	2/7		0.93%	0.74[0.17,3.17]

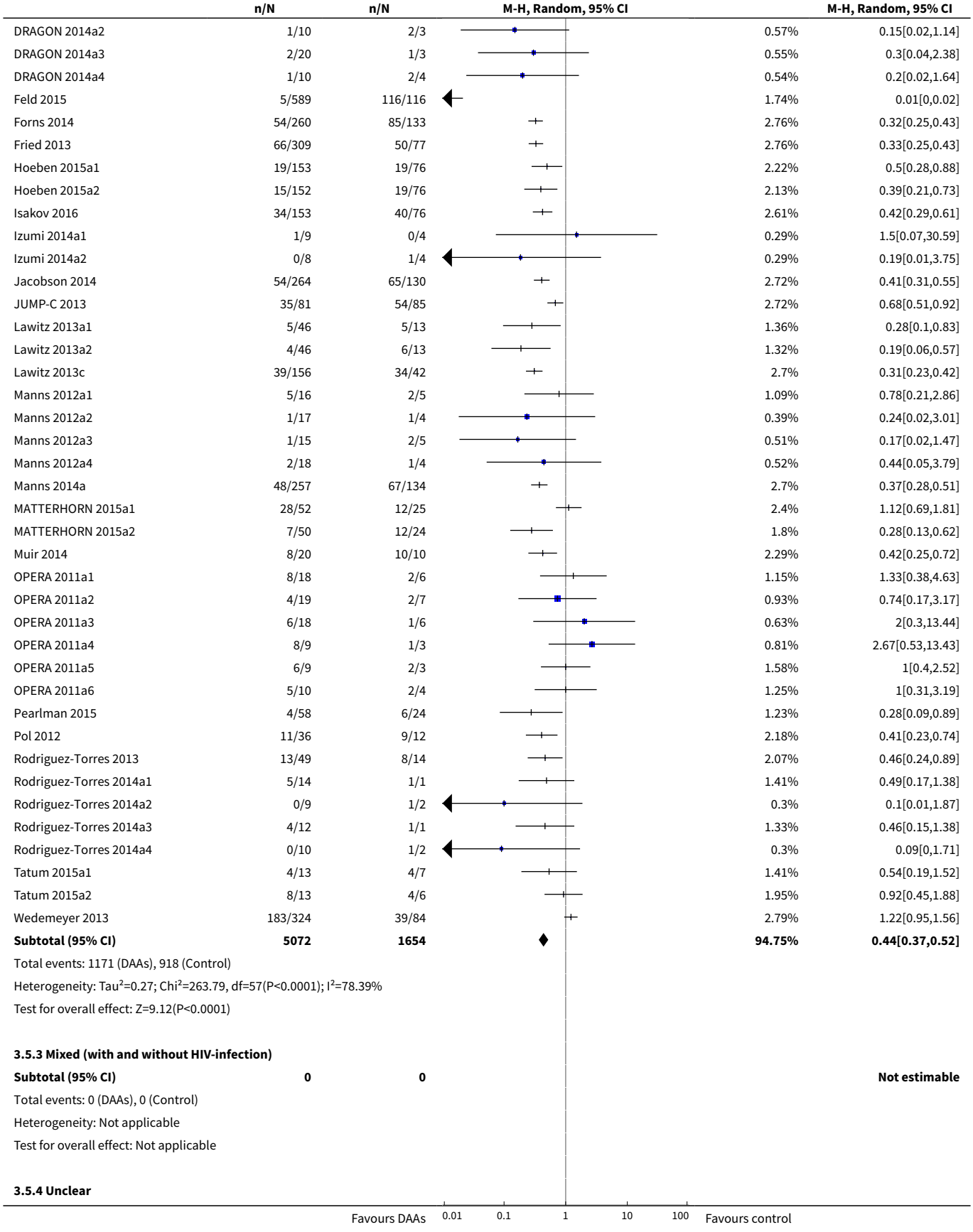




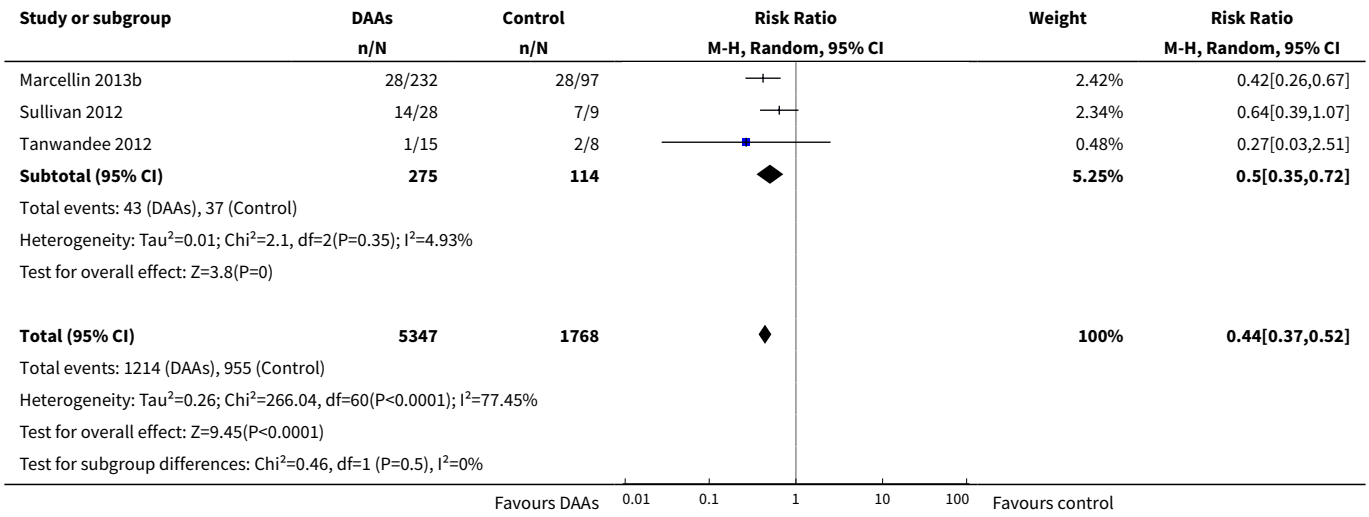


Analysis 3.5. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 5 Without sustained virological response - according to HIV-infection.

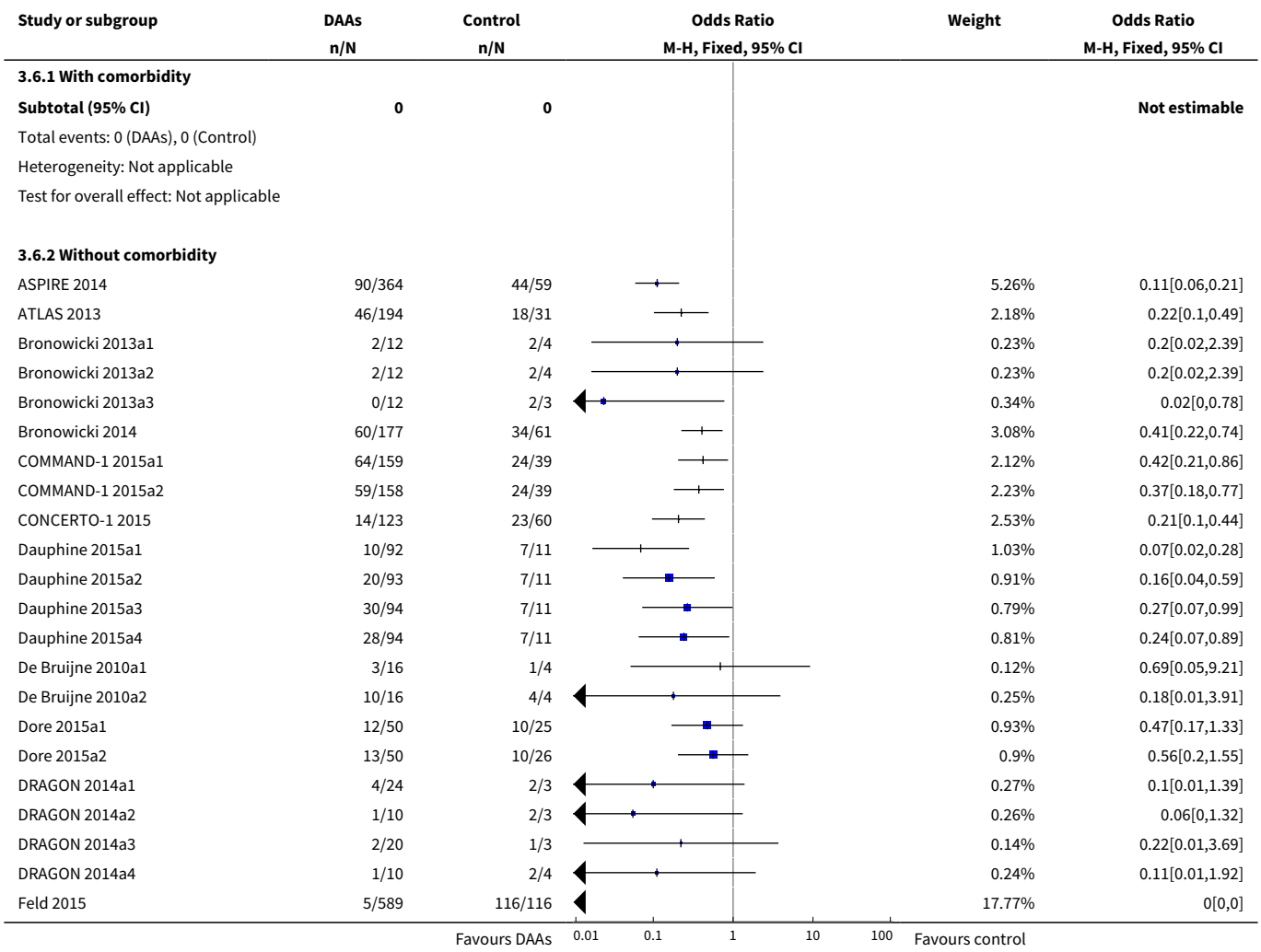


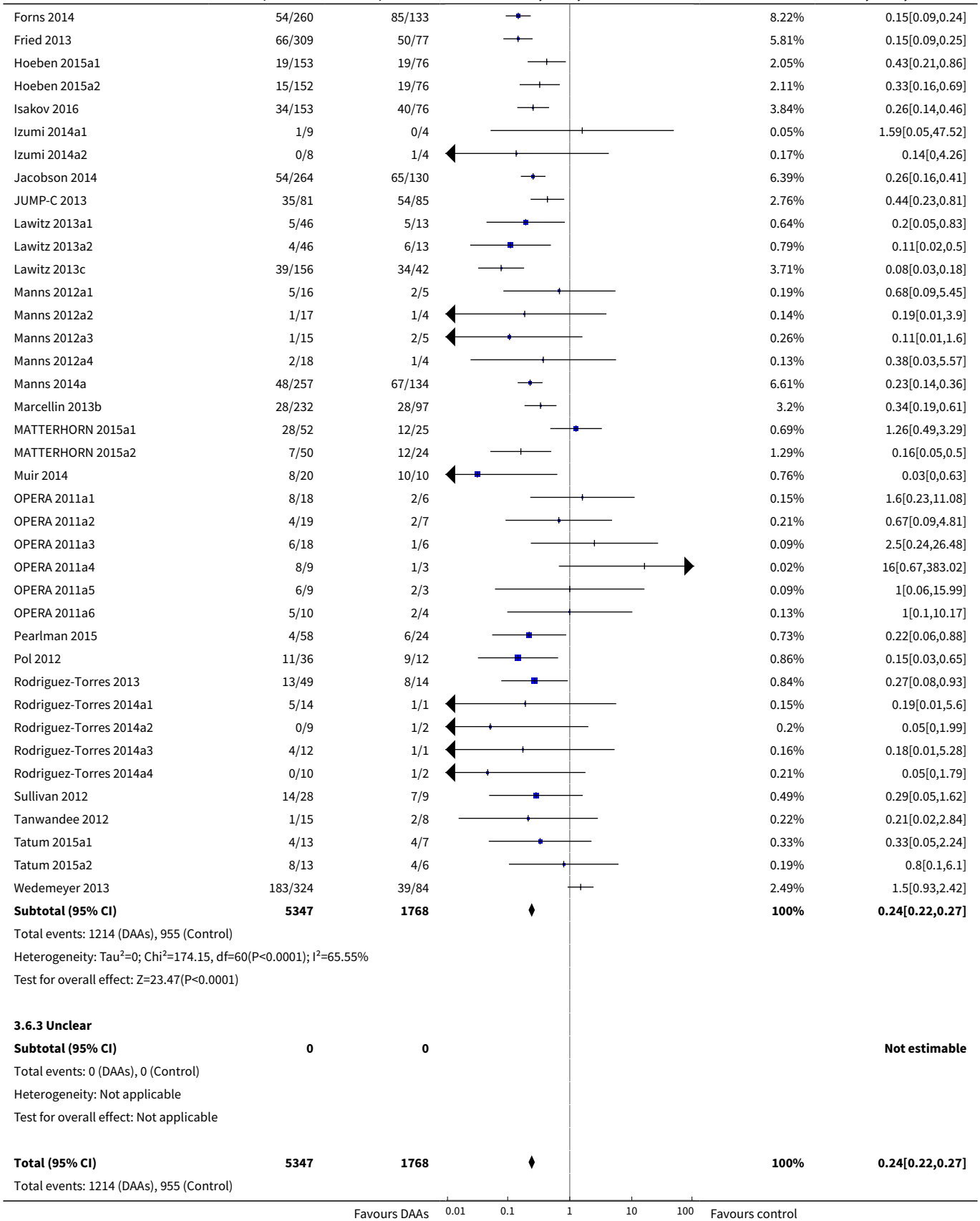


Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DRAGON 2014a2	1/10	2/3		0.57%	0.15[0.02,1.14]
DRAGON 2014a3	2/20	1/3		0.55%	0.3[0.04,2.38]
DRAGON 2014a4	1/10	2/4		0.54%	0.2[0.02,1.64]
Feld 2015	5/589	116/116		1.74%	0.01[0,0.02]
Forns 2014	54/260	85/133		2.76%	0.32[0.25,0.43]
Fried 2013	66/309	50/77		2.76%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.22%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		2.13%	0.39[0.21,0.73]
Isakov 2016	34/153	40/76		2.61%	0.42[0.29,0.61]
Izumi 2014a1	1/9	0/4		0.29%	1.5[0.07,30.59]
Izumi 2014a2	0/8	1/4		0.29%	0.19[0.01,3.75]
Jacobson 2014	54/264	65/130		2.72%	0.41[0.31,0.55]
JUMP-C 2013	35/81	54/85		2.72%	0.68[0.51,0.92]
Lawitz 2013a1	5/46	5/13		1.36%	0.28[0.1,0.83]
Lawitz 2013a2	4/46	6/13		1.32%	0.19[0.06,0.57]
Lawitz 2013c	39/156	34/42		2.7%	0.31[0.23,0.42]
Manns 2012a1	5/16	2/5		1.09%	0.78[0.21,2.86]
Manns 2012a2	1/17	1/4		0.39%	0.24[0.02,3.01]
Manns 2012a3	1/15	2/5		0.51%	0.17[0.02,1.47]
Manns 2012a4	2/18	1/4		0.52%	0.44[0.05,3.79]
Manns 2014a	48/257	67/134		2.7%	0.37[0.28,0.51]
MATTERHORN 2015a1	28/52	12/25		2.4%	1.12[0.69,1.81]
MATTERHORN 2015a2	7/50	12/24		1.8%	0.28[0.13,0.62]
Muir 2014	8/20	10/10		2.29%	0.42[0.25,0.72]
OPERA 2011a1	8/18	2/6		1.15%	1.33[0.38,4.63]
OPERA 2011a2	4/19	2/7		0.93%	0.74[0.17,3.17]
OPERA 2011a3	6/18	1/6		0.63%	2[0.3,13.44]
OPERA 2011a4	8/9	1/3		0.81%	2.67[0.53,13.43]
OPERA 2011a5	6/9	2/3		1.58%	1[0.4,2.52]
OPERA 2011a6	5/10	2/4		1.25%	1[0.31,3.19]
Pearlman 2015	4/58	6/24		1.23%	0.28[0.09,0.89]
Pol 2012	11/36	9/12		2.18%	0.41[0.23,0.74]
Rodriguez-Torres 2013	13/49	8/14		2.07%	0.46[0.24,0.89]
Rodriguez-Torres 2014a1	5/14	1/1		1.41%	0.49[0.17,1.38]
Rodriguez-Torres 2014a2	0/9	1/2		0.3%	0.1[0.01,1.87]
Rodriguez-Torres 2014a3	4/12	1/1		1.33%	0.46[0.15,1.38]
Rodriguez-Torres 2014a4	0/10	1/2		0.3%	0.09[0,1.71]
Tatum 2015a1	4/13	4/7		1.41%	0.54[0.19,1.52]
Tatum 2015a2	8/13	4/6		1.95%	0.92[0.45,1.88]
Wedemeyer 2013	183/324	39/84		2.79%	1.22[0.95,1.56]
Subtotal (95% CI)	**5072**	**1654**		**94.75%**	**0.44[0.37,0.52]**
Total events: 1171 (DAAs), 918 (Control)					
Heterogeneity: Tau^2=0.27; Chi^2=263.79, df=57(P<0.0001); I^2=78.39%					
Test for overall effect: Z=9.12(P<0.0001)					
3.5.3 Mixed (with and without HIV-infection)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.5.4 Unclear					



Analysis 3.6. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 6 Without sustained virological response - according to comorbidity.





Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Forns 2014	54/260	85/133		8.22%	0.15[0.09,0.24]
Fried 2013	66/309	50/77		5.81%	0.15[0.09,0.25]
Hoeben 2015a1	19/153	19/76		2.05%	0.43[0.21,0.86]
Hoeben 2015a2	15/152	19/76		2.11%	0.33[0.16,0.69]
Isakov 2016	34/153	40/76		3.84%	0.26[0.14,0.46]
Izumi 2014a1	1/9	0/4		0.05%	1.59[0.05,47.52]
Izumi 2014a2	0/8	1/4		0.17%	0.14[0,4.26]
Jacobson 2014	54/264	65/130		6.39%	0.26[0.16,0.41]
JUMP-C 2013	35/81	54/85		2.76%	0.44[0.23,0.81]
Lawitz 2013a1	5/46	5/13		0.64%	0.2[0.05,0.83]
Lawitz 2013a2	4/46	6/13		0.79%	0.11[0.02,0.5]
Lawitz 2013c	39/156	34/42		3.71%	0.08[0.03,0.18]
Manns 2012a1	5/16	2/5		0.19%	0.68[0.09,5.45]
Manns 2012a2	1/17	1/4		0.14%	0.19[0.01,3.9]
Manns 2012a3	1/15	2/5		0.26%	0.11[0.01,1.6]
Manns 2012a4	2/18	1/4		0.13%	0.38[0.03,5.57]
Manns 2014a	48/257	67/134		6.61%	0.23[0.14,0.36]
Marcellin 2013b	28/232	28/97		3.2%	0.34[0.19,0.61]
MATTERHORN 2015a1	28/52	12/25		0.69%	1.26[0.49,3.29]
MATTERHORN 2015a2	7/50	12/24		1.29%	0.16[0.05,0.5]
Muir 2014	8/20	10/10		0.76%	0.03[0,0.63]
OPERA 2011a1	8/18	2/6		0.15%	1.6[0.23,11.08]
OPERA 2011a2	4/19	2/7		0.21%	0.67[0.09,4.81]
OPERA 2011a3	6/18	1/6		0.09%	2.5[0.24,26.48]
OPERA 2011a4	8/9	1/3		0.02%	16[0.67,383.02]
OPERA 2011a5	6/9	2/3		0.09%	1[0.06,15.99]
OPERA 2011a6	5/10	2/4		0.13%	1[0.1,10.17]
Pearlman 2015	4/58	6/24		0.73%	0.22[0.06,0.88]
Pol 2012	11/36	9/12		0.86%	0.15[0.03,0.65]
Rodriguez-Torres 2013	13/49	8/14		0.84%	0.27[0.08,0.93]
Rodriguez-Torres 2014a1	5/14	1/1		0.15%	0.19[0.01,5.6]
Rodriguez-Torres 2014a2	0/9	1/2		0.2%	0.05[0,1.99]
Rodriguez-Torres 2014a3	4/12	1/1		0.16%	0.18[0.01,5.28]
Rodriguez-Torres 2014a4	0/10	1/2		0.21%	0.05[0,1.79]
Sullivan 2012	14/28	7/9		0.49%	0.29[0.05,1.62]
Tanwandee 2012	1/15	2/8		0.22%	0.21[0.02,2.84]
Tatum 2015a1	4/13	4/7		0.33%	0.33[0.05,2.24]
Tatum 2015a2	8/13	4/6		0.19%	0.8[0.1,6.1]
Wedemeyer 2013	183/324	39/84		2.49%	1.5[0.93,2.42]
Subtotal (95% CI)	**5347**	**1768**		**100%**	**0.24[0.22,0.27]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau²=0; Chi²=174.15, df=60(P<0.0001); I²=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
3.6.3 Unclear					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**5347**	**1768**		**100%**	**0.24[0.22,0.27]**
Total events: 1214 (DAAs), 955 (Control)					

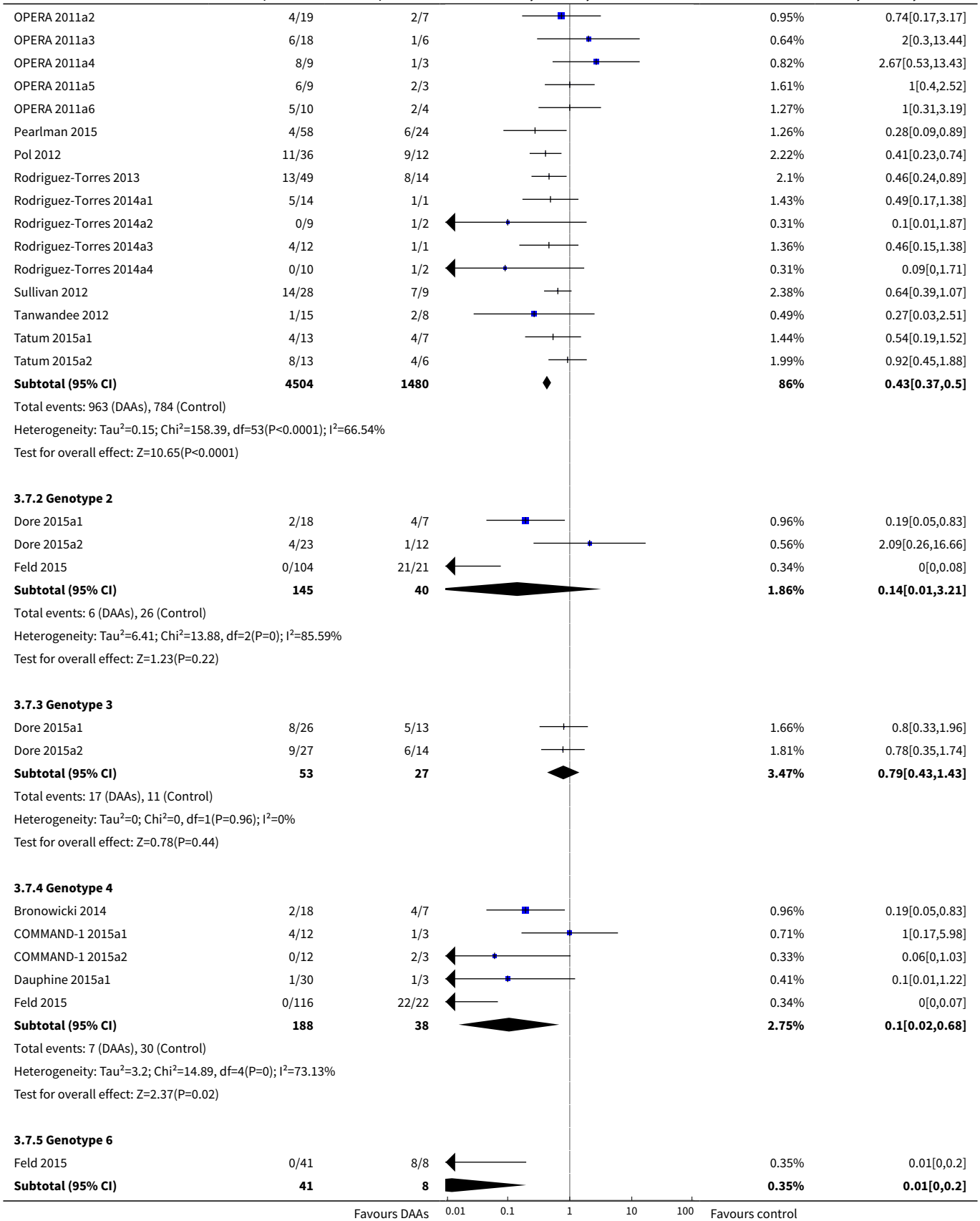
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=174.15, df=60(P<0.0001); I²=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
Test for subgroup differences: Not applicable					

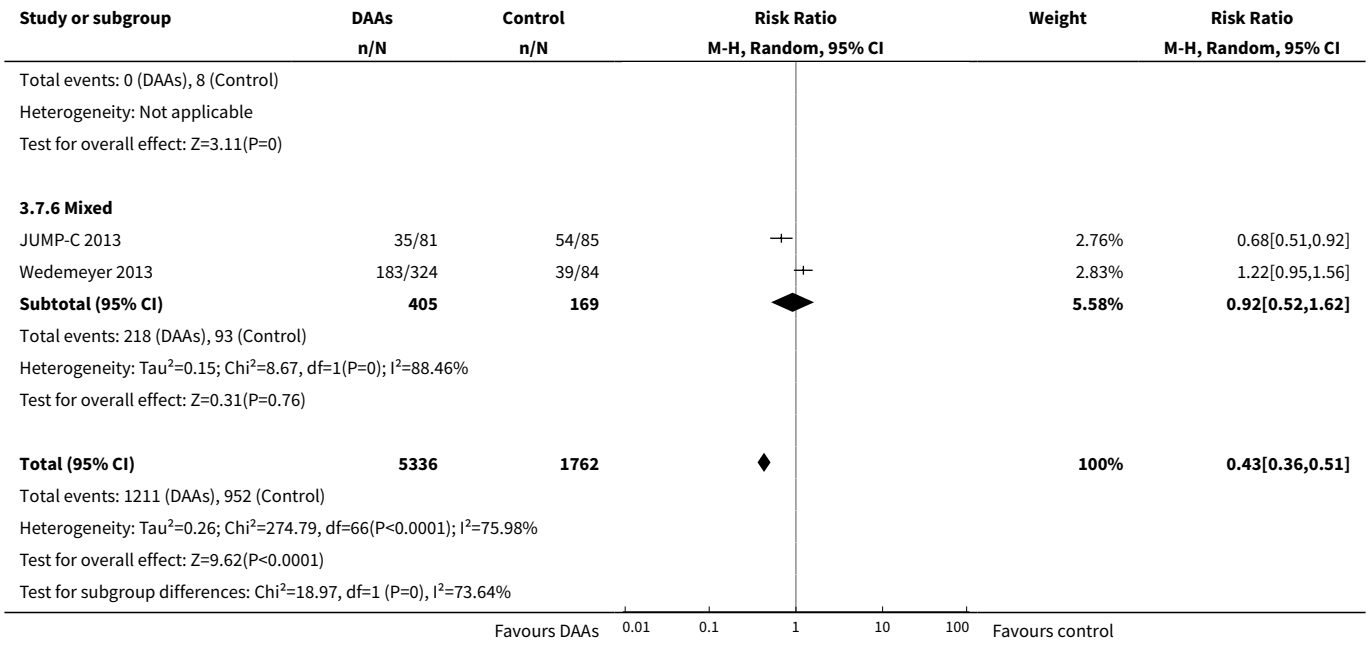
Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 3.7. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 7 Without sustained virological response - according to viral genotype.

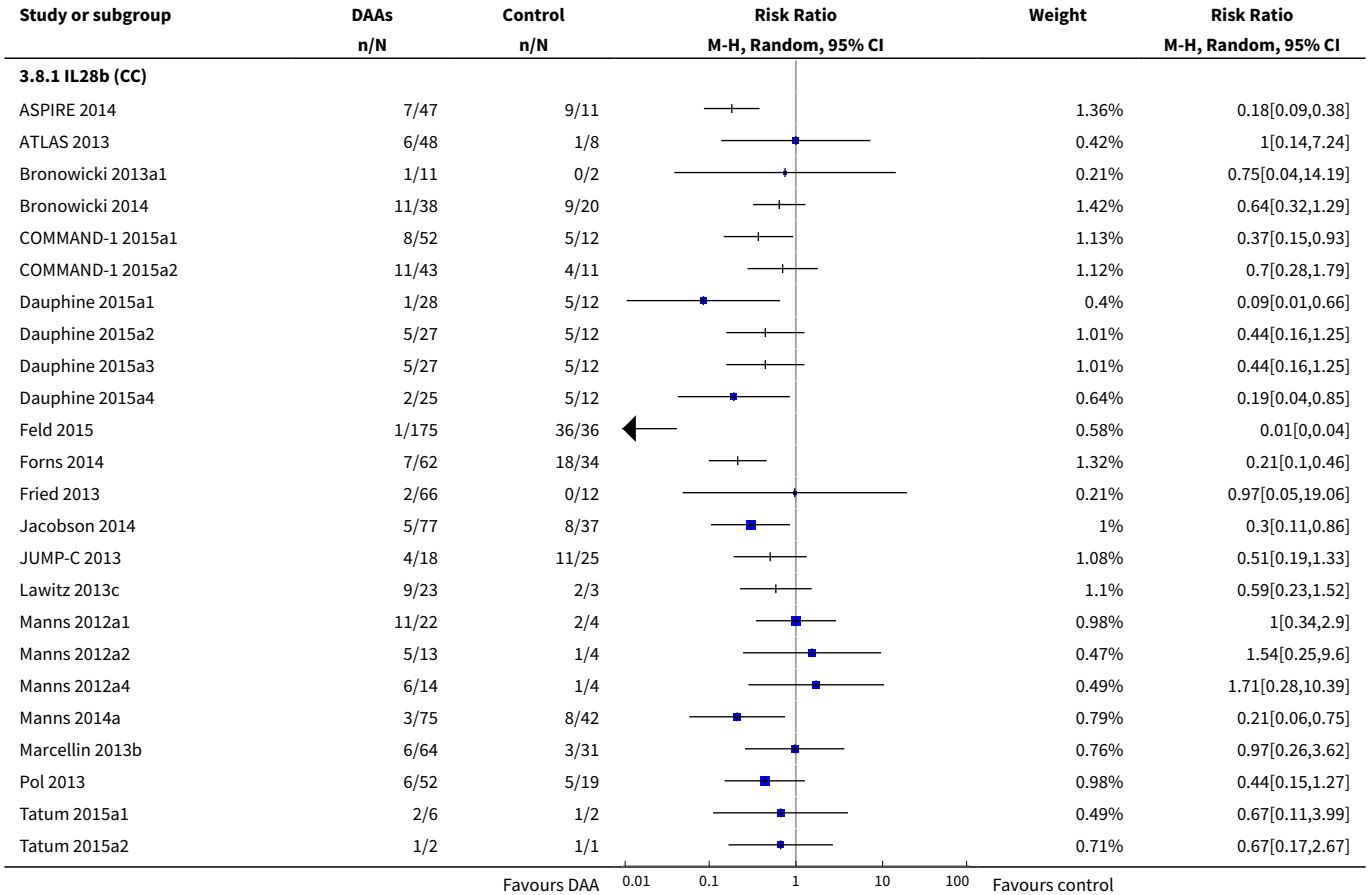
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 Genotype 1					
ASPIRE 2014	90/364	44/59		2.85%	0.33[0.26,0.42]
ATLAS 2013	46/194	18/31		2.6%	0.41[0.28,0.6]
Bronowicki 2013a1	2/12	2/4		0.84%	0.33[0.07,1.65]
Bronowicki 2013a2	2/12	2/4		0.84%	0.33[0.07,1.65]
Bronowicki 2013a3	0/12	2/3		0.33%	0.06[0,1.03]
Bronowicki 2014	58/159	30/54		2.73%	0.66[0.48,0.9]
COMMAND-1 2015a1	60/147	24/36		2.75%	0.61[0.45,0.83]
COMMAND-1 2015a2	58/145	23/36		2.73%	0.63[0.46,0.86]
CONCERTO-1 2015	14/123	23/60		2.22%	0.3[0.16,0.53]
Dauphine 2015a1	87/339	26/40		2.77%	0.39[0.3,0.53]
De Bruijne 2010a1	3/16	1/4		0.61%	0.75[0.1,5.43]
De Bruijne 2010a2	10/16	4/4		2.45%	0.69[0.43,1.1]
DRAGON 2014a1	4/24	2/3		1.22%	0.25[0.08,0.83]
DRAGON 2014a2	1/10	2/3		0.58%	0.15[0.02,1.14]
DRAGON 2014a3	2/20	1/3		0.56%	0.3[0.04,2.38]
DRAGON 2014a4	1/10	2/4		0.55%	0.2[0.02,1.64]
Feld 2015	5/328	65/65		1.77%	0.02[0.01,0.04]
Forns 2014	54/260	85/133		2.8%	0.32[0.25,0.43]
Fried 2013	66/309	50/77		2.8%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.25%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		2.17%	0.39[0.21,0.73]
Isakov 2016	34/153	40/76		2.65%	0.42[0.29,0.61]
Izumi 2014a1	1/9	0/4		0.29%	1.5[0.07,30.59]
Izumi 2014a2	0/8	1/4		0.3%	0.19[0.01,3.75]
Jacobson 2014	54/264	65/130		2.76%	0.41[0.31,0.55]
Lawitz 2013a1	5/46	5/13		1.38%	0.28[0.1,0.83]
Lawitz 2013a2	4/46	6/13		1.34%	0.19[0.06,0.57]
Lawitz 2013c	39/156	34/42		2.74%	0.31[0.23,0.42]
Manns 2012a1	5/16	2/5		1.11%	0.78[0.21,2.86]
Manns 2012a2	1/17	1/4		0.4%	0.24[0.02,3.01]
Manns 2012a3	1/15	2/5		0.52%	0.17[0.02,1.47]
Manns 2012a4	2/18	1/4		0.53%	0.44[0.05,3.79]
Manns 2014a	48/257	67/134		2.74%	0.37[0.28,0.51]
Marcellin 2013b	28/232	28/97		2.46%	0.42[0.26,0.67]
MATTERHORN 2015a1	28/52	12/25		2.44%	1.12[0.69,1.81]
MATTERHORN 2015a2	7/50	12/24		1.83%	0.28[0.13,0.62]
Muir 2014	8/20	10/10		2.33%	0.42[0.25,0.72]
OPERA 2011a1	8/18	2/6		1.17%	1.33[0.38,4.63]

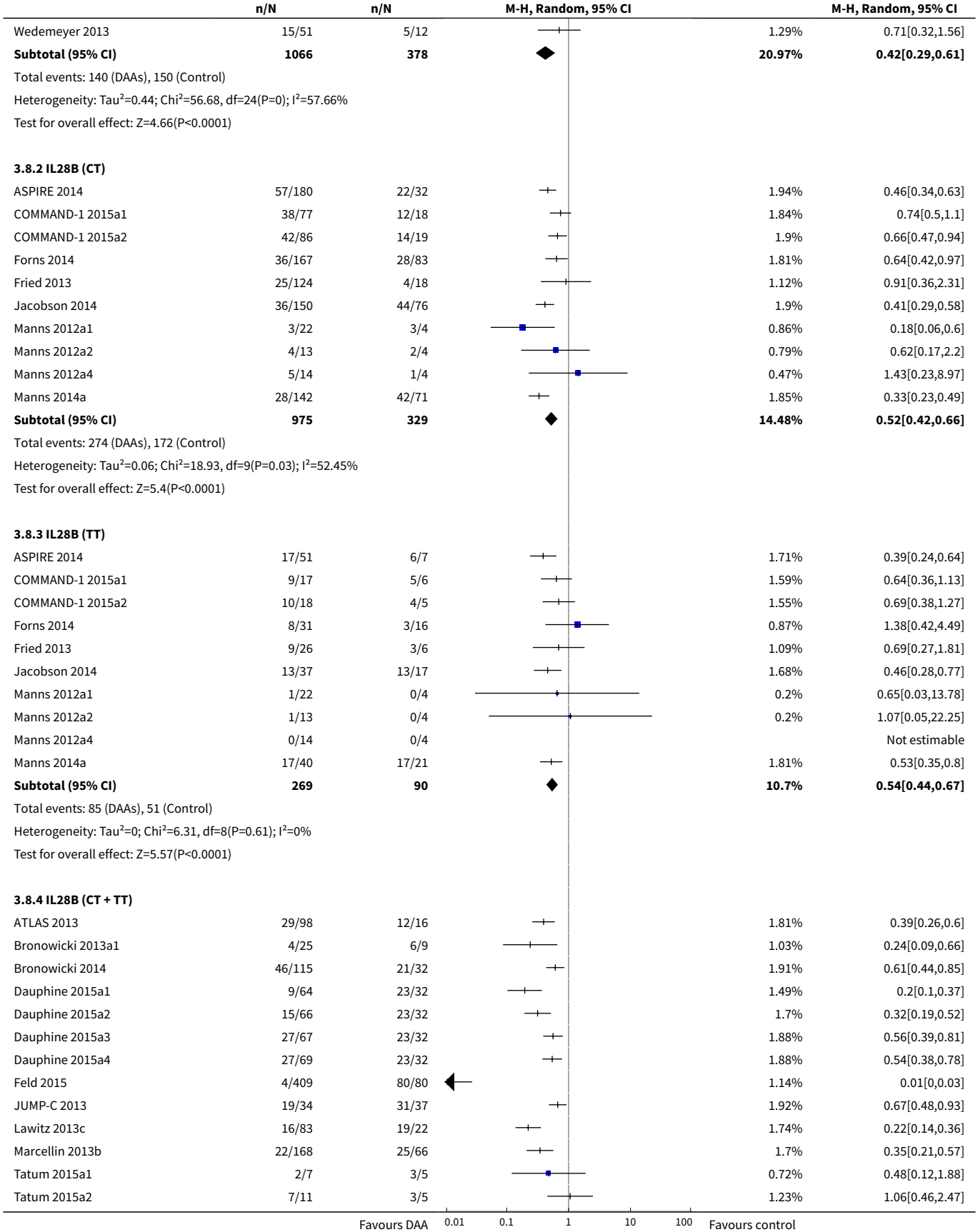
Favours DAAs 0.01 0.1 1 10 100 Favours control



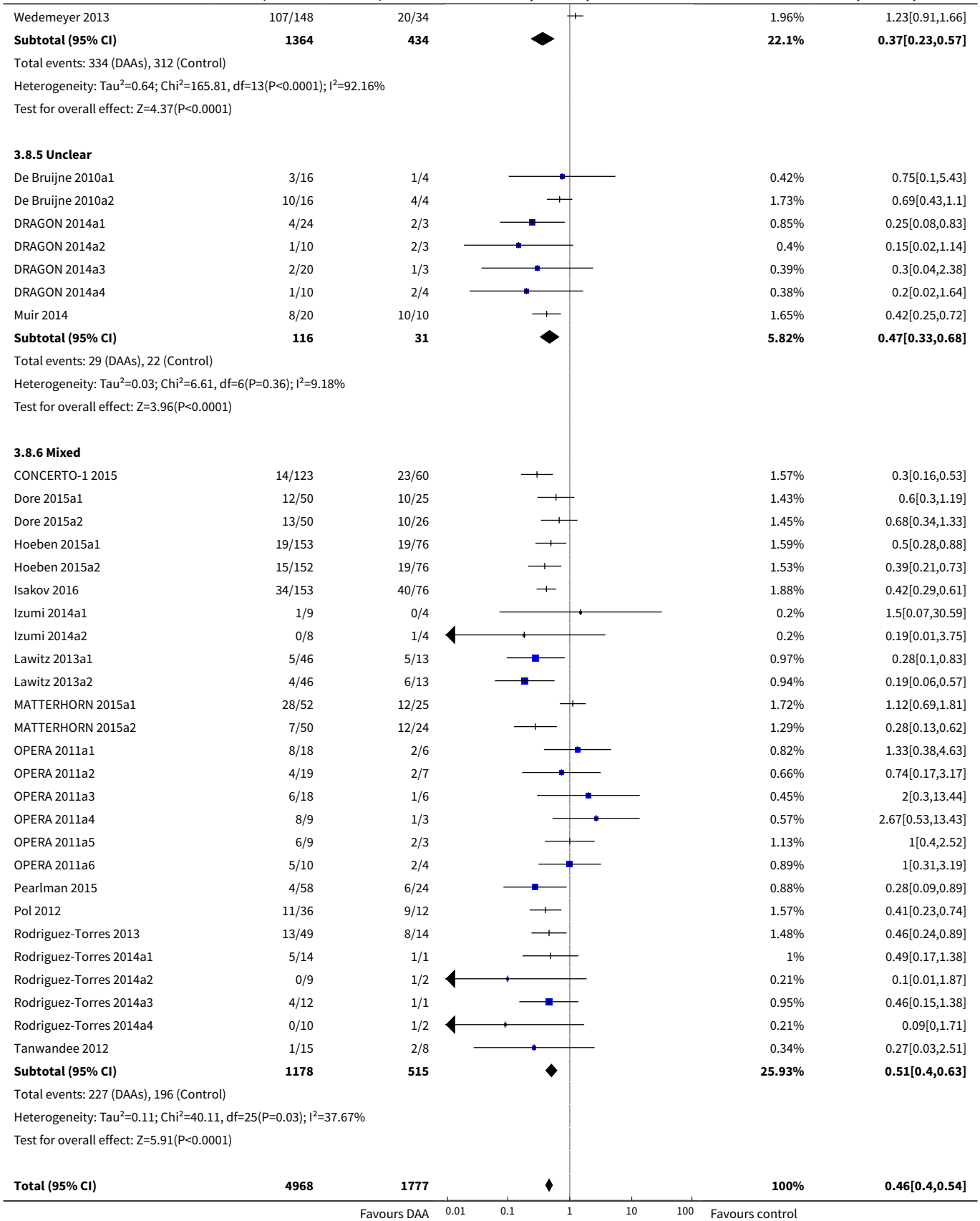


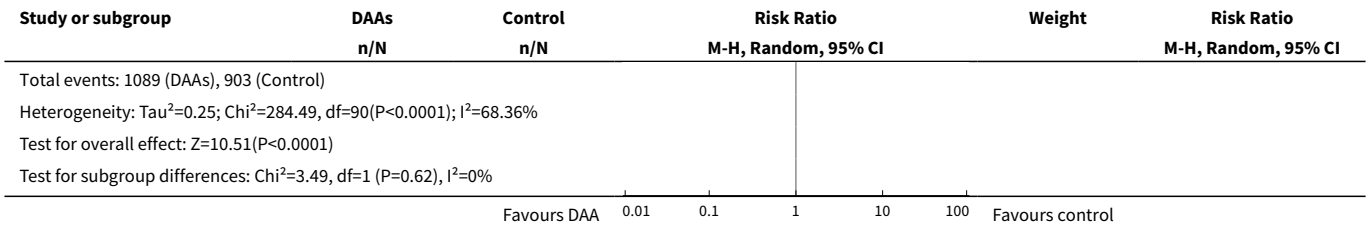
Analysis 3.8. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 8 Without sustained virological response - according to human genotype (IL28b).





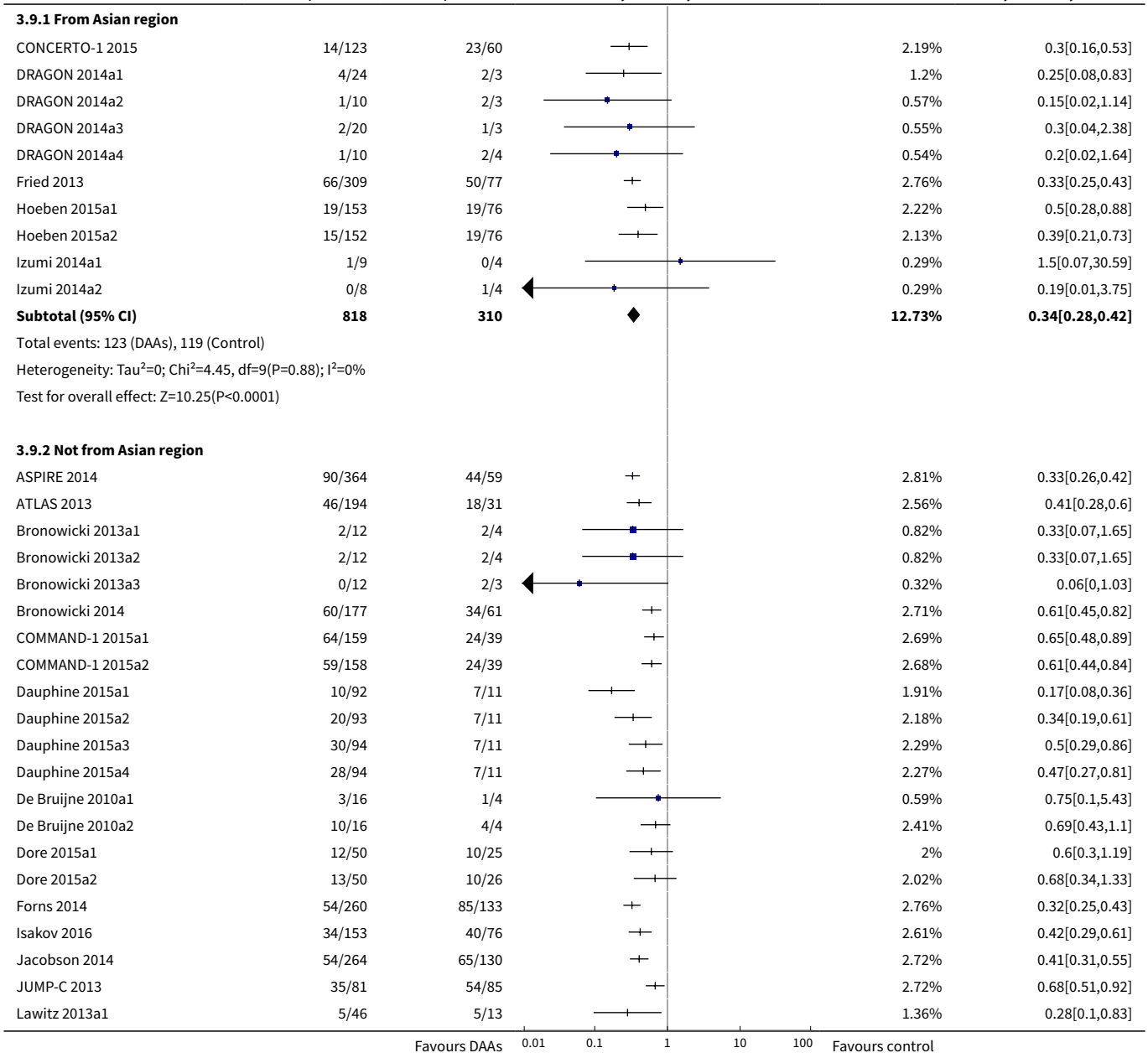
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Wedemeyer 2013	15/51	5/12		1.29%	0.71[0.32,1.56]
Subtotal (95% CI)	**1066**	**378**		**20.97%**	**0.42[0.29,0.61]**
Total events: 140 (DAAs), 150 (Control)					
Heterogeneity: Tau²=0.44; Chi²=56.68, df=24(P=0); I²=57.66%					
Test for overall effect: Z=4.66(P<0.0001)					
3.8.2 IL28B (CT)					
ASPIRE 2014	57/180	22/32		1.94%	0.46[0.34,0.63]
COMMAND-1 2015a1	38/77	12/18		1.84%	0.74[0.5,1.1]
COMMAND-1 2015a2	42/86	14/19		1.9%	0.66[0.47,0.94]
Forns 2014	36/167	28/83		1.81%	0.64[0.42,0.97]
Fried 2013	25/124	4/18		1.12%	0.91[0.36,2.31]
Jacobson 2014	36/150	44/76		1.9%	0.41[0.29,0.58]
Manns 2012a1	3/22	3/4		0.86%	0.18[0.06,0.6]
Manns 2012a2	4/13	2/4		0.79%	0.62[0.17,2.2]
Manns 2012a4	5/14	1/4		0.47%	1.43[0.23,8.97]
Manns 2014a	28/142	42/71		1.85%	0.33[0.23,0.49]
Subtotal (95% CI)	**975**	**329**		**14.48%**	**0.52[0.42,0.66]**
Total events: 274 (DAAs), 172 (Control)					
Heterogeneity: Tau²=0.06; Chi²=18.93, df=9(P=0.03); I²=52.45%					
Test for overall effect: Z=5.4(P<0.0001)					
3.8.3 IL28B (TT)					
ASPIRE 2014	17/51	6/7		1.71%	0.39[0.24,0.64]
COMMAND-1 2015a1	9/17	5/6		1.59%	0.64[0.36,1.13]
COMMAND-1 2015a2	10/18	4/5		1.55%	0.69[0.38,1.27]
Forns 2014	8/31	3/16		0.87%	1.38[0.42,4.49]
Fried 2013	9/26	3/6		1.09%	0.69[0.27,1.81]
Jacobson 2014	13/37	13/17		1.68%	0.46[0.28,0.77]
Manns 2012a1	1/22	0/4		0.2%	0.65[0.03,13.78]
Manns 2012a2	1/13	0/4		0.2%	1.07[0.05,22.25]
Manns 2012a4	0/14	0/4			Not estimable
Manns 2014a	17/40	17/21		1.81%	0.53[0.35,0.8]
Subtotal (95% CI)	**269**	**90**		**10.7%**	**0.54[0.44,0.67]**
Total events: 85 (DAAs), 51 (Control)					
Heterogeneity: Tau²=0; Chi²=6.31, df=8(P=0.61); I²=0%					
Test for overall effect: Z=5.57(P<0.0001)					
3.8.4 IL28B (CT + TT)					
ATLAS 2013	29/98	12/16		1.81%	0.39[0.26,0.6]
Bronowicki 2013a1	4/25	6/9		1.03%	0.24[0.09,0.66]
Bronowicki 2014	46/115	21/32		1.91%	0.61[0.44,0.85]
Dauphine 2015a1	9/64	23/32		1.49%	0.2[0.1,0.37]
Dauphine 2015a2	15/66	23/32		1.7%	0.32[0.19,0.52]
Dauphine 2015a3	27/67	23/32		1.88%	0.56[0.39,0.81]
Dauphine 2015a4	27/69	23/32		1.88%	0.54[0.38,0.78]
Feld 2015	4/409	80/80		1.14%	0.01[0,0.03]
JUMP-C 2013	19/34	31/37		1.92%	0.67[0.48,0.93]
Lawitz 2013c	16/83	19/22		1.74%	0.22[0.14,0.36]
Marcellin 2013b	22/168	25/66		1.7%	0.35[0.21,0.57]
Tatum 2015a1	2/7	3/5		0.72%	0.48[0.12,1.88]
Tatum 2015a2	7/11	3/5		1.23%	1.06[0.46,2.47]

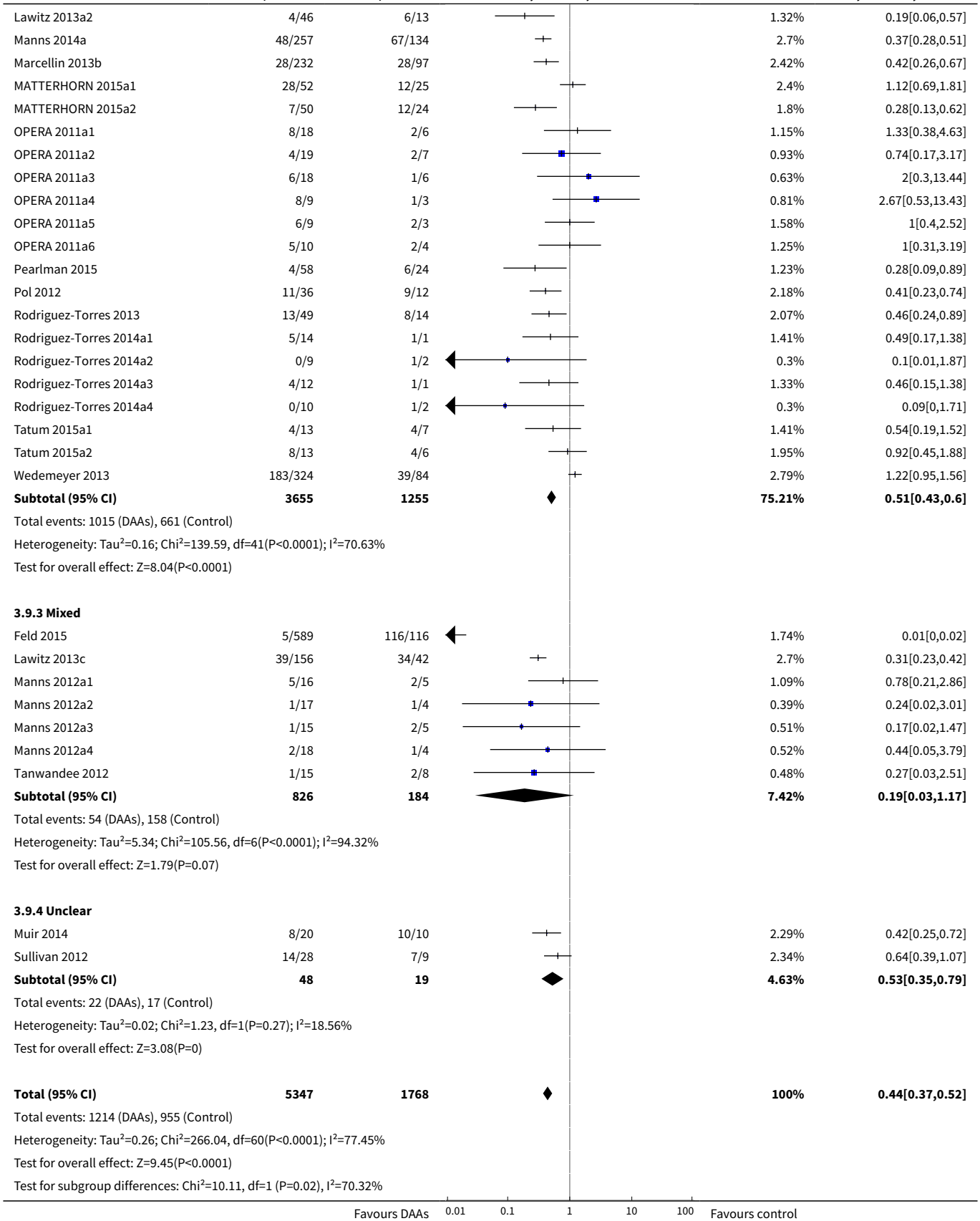




Analysis 3.9. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 9 Without sustained virological response - according to Asian-region.

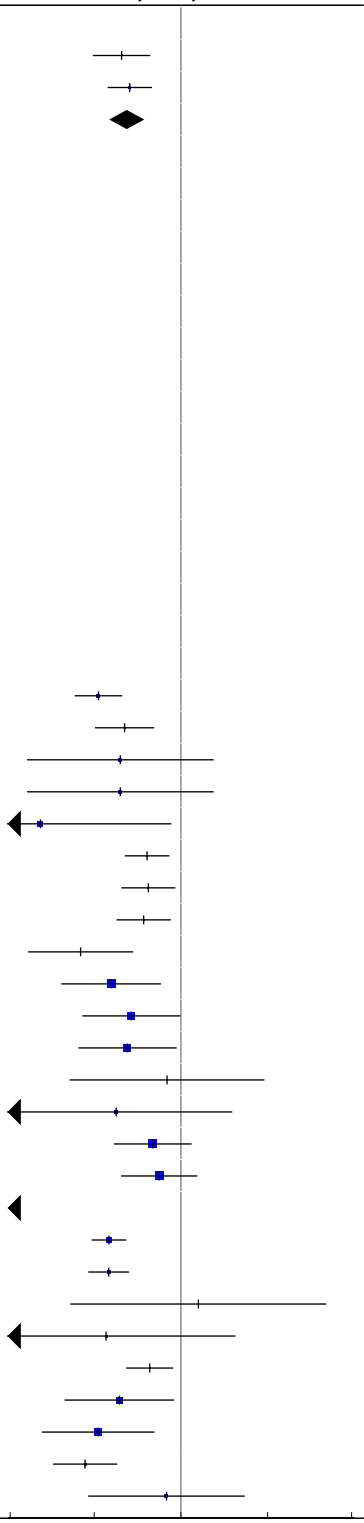
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 From Asian region					
CONCERTO-1 2015	14/123	23/60		2.19%	0.3[0.16,0.53]
DRAGON 2014a1	4/24	2/3		1.2%	0.25[0.08,0.83]
DRAGON 2014a2	1/10	2/3		0.57%	0.15[0.02,1.14]
DRAGON 2014a3	2/20	1/3		0.55%	0.3[0.04,2.38]
DRAGON 2014a4	1/10	2/4		0.54%	0.2[0.02,1.64]
Fried 2013	66/309	50/77		2.76%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.22%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		2.13%	0.39[0.21,0.73]
Izumi 2014a1	1/9	0/4		0.29%	1.5[0.07,30.59]
Izumi 2014a2	0/8	1/4		0.29%	0.19[0.01,3.75]
Subtotal (95% CI)	**818**	**310**		**12.73%**	**0.34[0.28,0.42]**
Total events: 123 (DAAs), 119 (Control)					
Heterogeneity: Tau²=0; Chi²=4.45, df=9(P=0.88); I²=0%					
Test for overall effect: Z=10.25(P<0.0001)					
3.9.2 Not from Asian region					
ASPIRE 2014	90/364	44/59		2.81%	0.33[0.26,0.42]
ATLAS 2013	46/194	18/31		2.56%	0.41[0.28,0.6]
Bronowicki 2013a1	2/12	2/4		0.82%	0.33[0.07,1.65]
Bronowicki 2013a2	2/12	2/4		0.82%	0.33[0.07,1.65]
Bronowicki 2013a3	0/12	2/3		0.32%	0.06[0,1.03]
Bronowicki 2014	60/177	34/61		2.71%	0.61[0.45,0.82]
COMMAND-1 2015a1	64/159	24/39		2.69%	0.65[0.48,0.89]
COMMAND-1 2015a2	59/158	24/39		2.68%	0.61[0.44,0.84]
Dauphine 2015a1	10/92	7/11		1.91%	0.17[0.08,0.36]
Dauphine 2015a2	20/93	7/11		2.18%	0.34[0.19,0.61]
Dauphine 2015a3	30/94	7/11		2.29%	0.5[0.29,0.86]
Dauphine 2015a4	28/94	7/11		2.27%	0.47[0.27,0.81]
De Bruijne 2010a1	3/16	1/4		0.59%	0.75[0.1,5.43]
De Bruijne 2010a2	10/16	4/4		2.41%	0.69[0.43,1.1]
Dore 2015a1	12/50	10/25		2%	0.6[0.3,1.19]
Dore 2015a2	13/50	10/26		2.02%	0.68[0.34,1.33]
Forns 2014	54/260	85/133		2.76%	0.32[0.25,0.43]
Isakov 2016	34/153	40/76		2.61%	0.42[0.29,0.61]
Jacobson 2014	54/264	65/130		2.72%	0.41[0.31,0.55]
JUMP-C 2013	35/81	54/85		2.72%	0.68[0.51,0.92]
Lawitz 2013a1	5/46	5/13		1.36%	0.28[0.1,0.83]

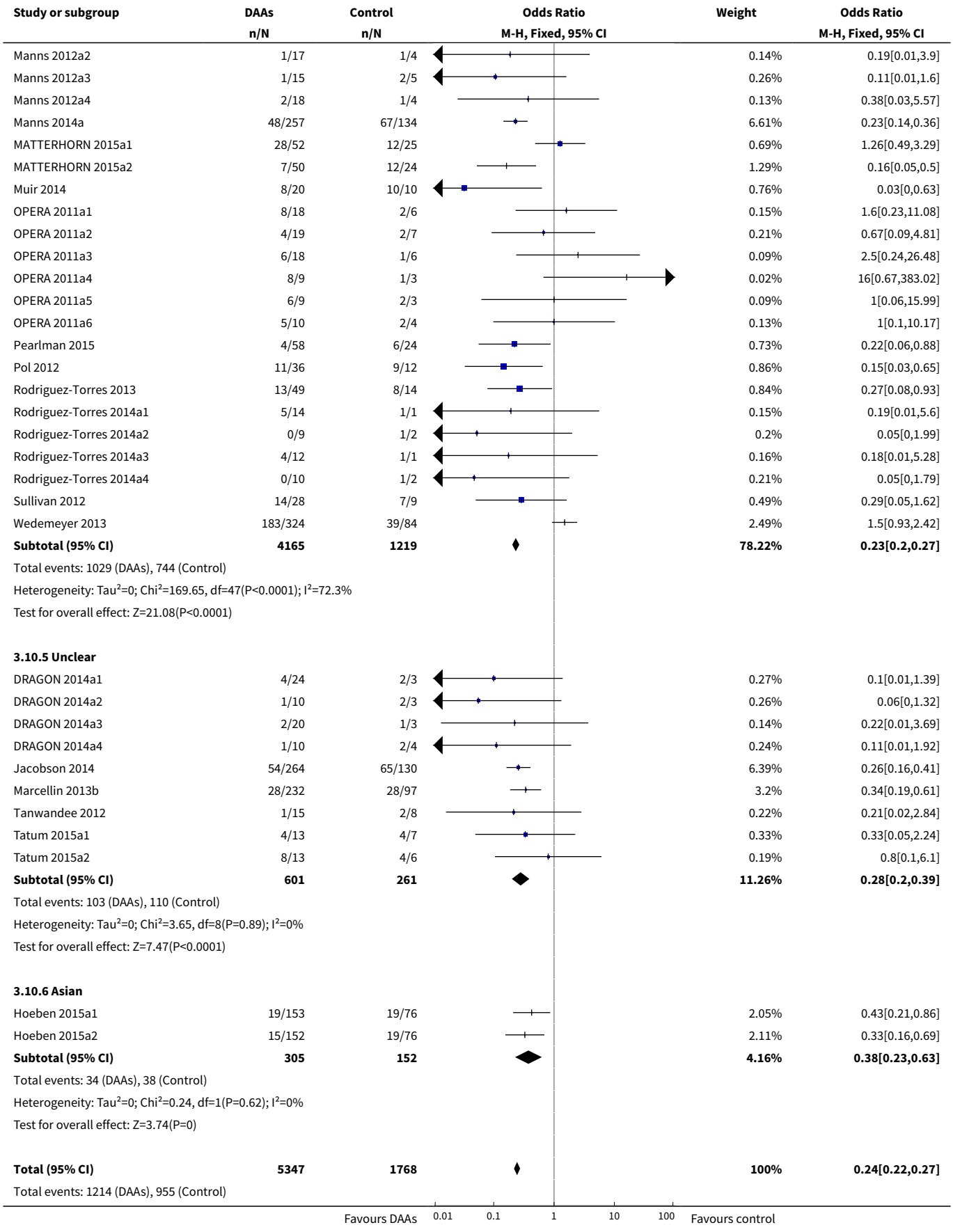




Analysis 3.10. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 10 Without sustained virological response - according to specific ethnicities.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.10.1 White					
CONCERTO-1 2015	14/123	23/60		2.53%	0.21[0.1,0.44]
Isakov 2016	34/153	40/76		3.84%	0.26[0.14,0.46]
Subtotal (95% CI)	**276**	**136**		**6.36%**	**0.24[0.15,0.38]**
Total events: 48 (DAAs), 63 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.66); I^2=0%					
Test for overall effect: Z=6.05(P<0.0001)					
3.10.2 Black					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.10.3 Hispanic					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.10.4 Mixed					
ASPIRE 2014	90/364	44/59		5.26%	0.11[0.06,0.21]
ATLAS 2013	46/194	18/31		2.18%	0.22[0.1,0.49]
Bronowicki 2013a1	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a2	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a3	0/12	2/3		0.34%	0.02[0,0.78]
Bronowicki 2014	60/177	34/61		3.08%	0.41[0.22,0.74]
COMMAND-1 2015a1	64/159	24/39		2.12%	0.42[0.21,0.86]
COMMAND-1 2015a2	59/158	24/39		2.23%	0.37[0.18,0.77]
Dauphine 2015a1	10/92	7/11		1.03%	0.07[0.02,0.28]
Dauphine 2015a2	20/93	7/11		0.91%	0.16[0.04,0.59]
Dauphine 2015a3	30/94	7/11		0.79%	0.27[0.07,0.99]
Dauphine 2015a4	28/94	7/11		0.81%	0.24[0.07,0.89]
De Bruijne 2010a1	3/16	1/4		0.12%	0.69[0.05,9.21]
De Bruijne 2010a2	10/16	4/4		0.25%	0.18[0.01,3.91]
Dore 2015a1	12/50	10/25		0.93%	0.47[0.17,1.33]
Dore 2015a2	13/50	10/26		0.9%	0.56[0.2,1.55]
Feld 2015	5/589	116/116		17.77%	0[0,0]
Forns 2014	54/260	85/133		8.22%	0.15[0.09,0.24]
Fried 2013	66/309	50/77		5.81%	0.15[0.09,0.25]
Izumi 2014a1	1/9	0/4		0.05%	1.59[0.05,47.52]
Izumi 2014a2	0/8	1/4		0.17%	0.14[0,4.26]
JUMP-C 2013	35/81	54/85		2.76%	0.44[0.23,0.81]
Lawitz 2013a1	5/46	5/13		0.64%	0.2[0.05,0.83]
Lawitz 2013a2	4/46	6/13		0.79%	0.11[0.02,0.5]
Lawitz 2013c	39/156	34/42		3.71%	0.08[0.03,0.18]
Manns 2012a1	5/16	2/5		0.19%	0.68[0.09,5.45]





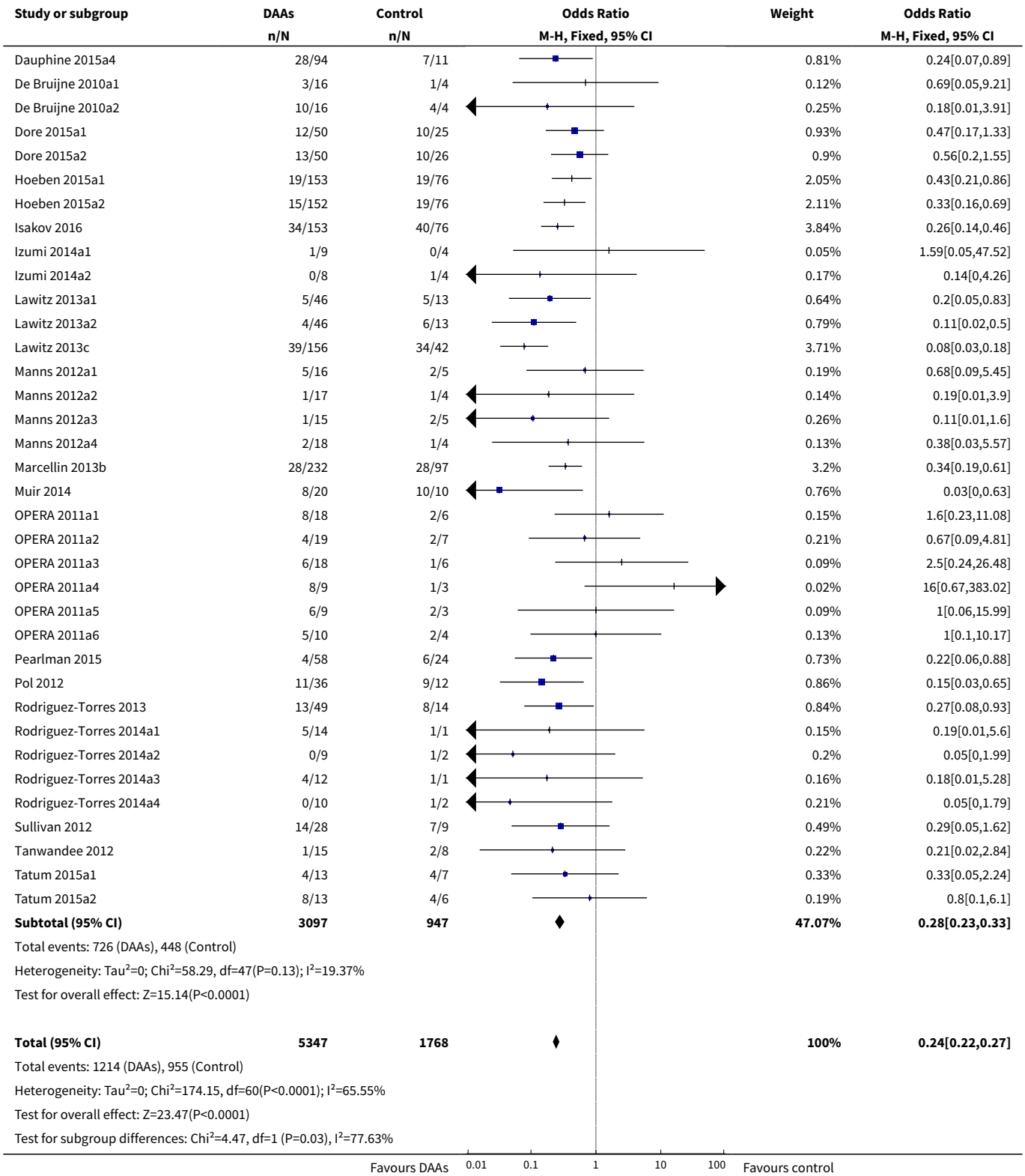
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=174.15, df=60(P<0.0001); I²=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
Test for subgroup differences: Chi²=3.91, df=1 (P=0.27), I²=23.33%					

Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 3.11. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 11 Without sustained virological response - according to reaching planned sample size.

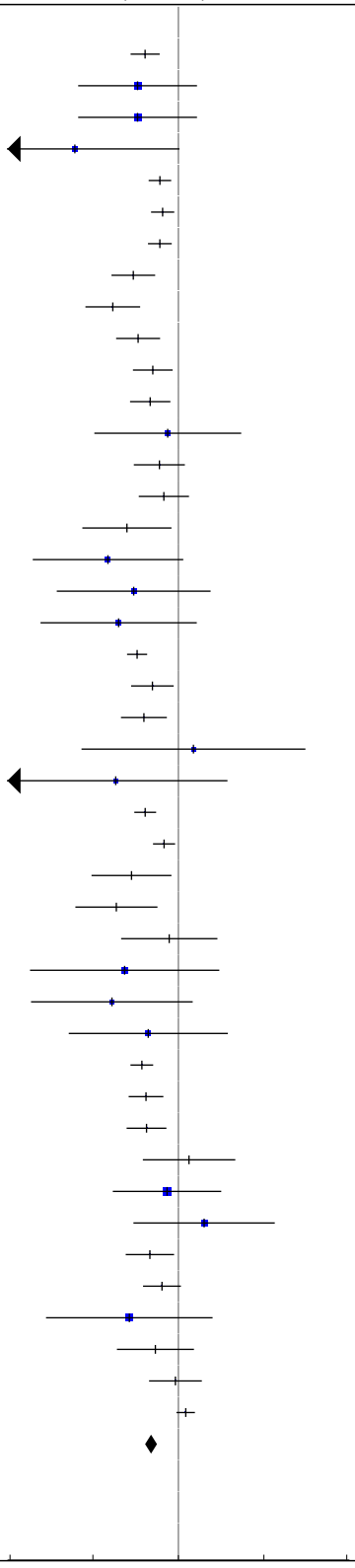
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.11.1 Trials reaching planned sample size					
DRAGON 2014a1	4/24	2/3		0.27%	0.1[0.01,1.39]
DRAGON 2014a2	1/10	2/3		0.26%	0.06[0,1.32]
DRAGON 2014a3	2/20	1/3		0.14%	0.22[0.01,3.69]
DRAGON 2014a4	1/10	2/4		0.24%	0.11[0.01,1.92]
Feld 2015	5/589	116/116		17.77%	0[0,0]
Forns 2014	54/260	85/133		8.22%	0.15[0.09,0.24]
Fried 2013	66/309	50/77		5.81%	0.15[0.09,0.25]
Jacobson 2014	54/264	65/130		6.39%	0.26[0.16,0.41]
JUMP-C 2013	35/81	54/85		2.76%	0.44[0.23,0.81]
Manns 2014a	48/257	67/134		6.61%	0.23[0.14,0.36]
MATTERHORN 2015a1	28/52	12/25		0.69%	1.26[0.49,3.29]
MATTERHORN 2015a2	7/50	12/24		1.29%	0.16[0.05,0.5]
Wedemeyer 2013	183/324	39/84		2.49%	1.5[0.93,2.42]
Subtotal (95% CI)	**2250**	**821**		**52.93%**	**0.21[0.18,0.25]**
Total events: 488 (DAAs), 507 (Control)					
Heterogeneity: Tau²=0; Chi²=120.88, df=12(P<0.0001); I²=90.07%					
Test for overall effect: Z=17.94(P<0.0001)					
3.11.2 Trials not reaching planned sample size					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.11.3 Unclear					
ASPIRE 2014	90/364	44/59		5.26%	0.11[0.06,0.21]
ATLAS 2013	46/194	18/31		2.18%	0.22[0.1,0.49]
Bronowicki 2013a1	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a2	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a3	0/12	2/3		0.34%	0.02[0,0.78]
Bronowicki 2014	60/177	34/61		3.08%	0.41[0.22,0.74]
COMMAND-1 2015a1	64/159	24/39		2.12%	0.42[0.21,0.86]
COMMAND-1 2015a2	59/158	24/39		2.23%	0.37[0.18,0.77]
CONCERTO-1 2015	14/123	23/60		2.53%	0.21[0.1,0.44]
Dauphine 2015a1	10/92	7/11		1.03%	0.07[0.02,0.28]
Dauphine 2015a2	20/93	7/11		0.91%	0.16[0.04,0.59]
Dauphine 2015a3	30/94	7/11		0.79%	0.27[0.07,0.99]

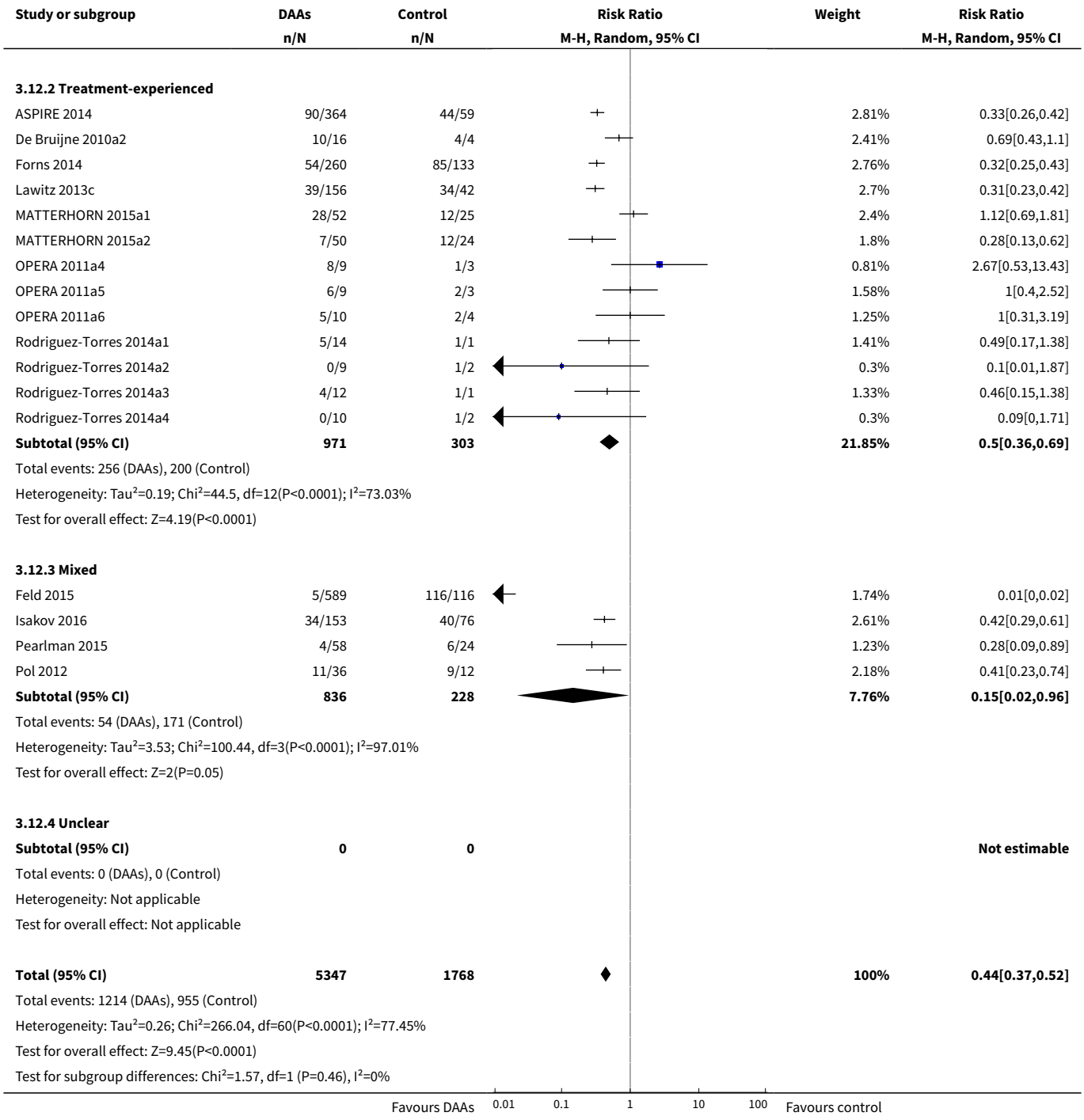
Favours DAAs 0.01 0.1 1 10 100 Favours control



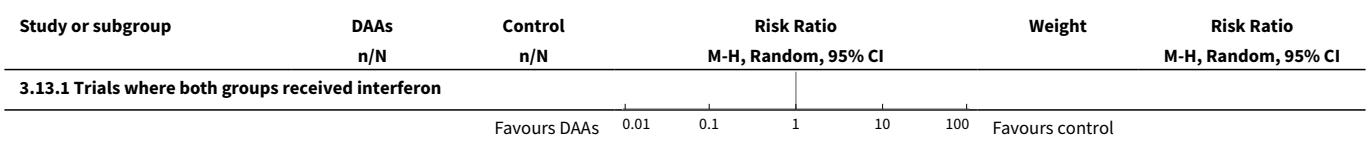
Analysis 3.12. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 12 Without sustained virological response - according to prior treatment.

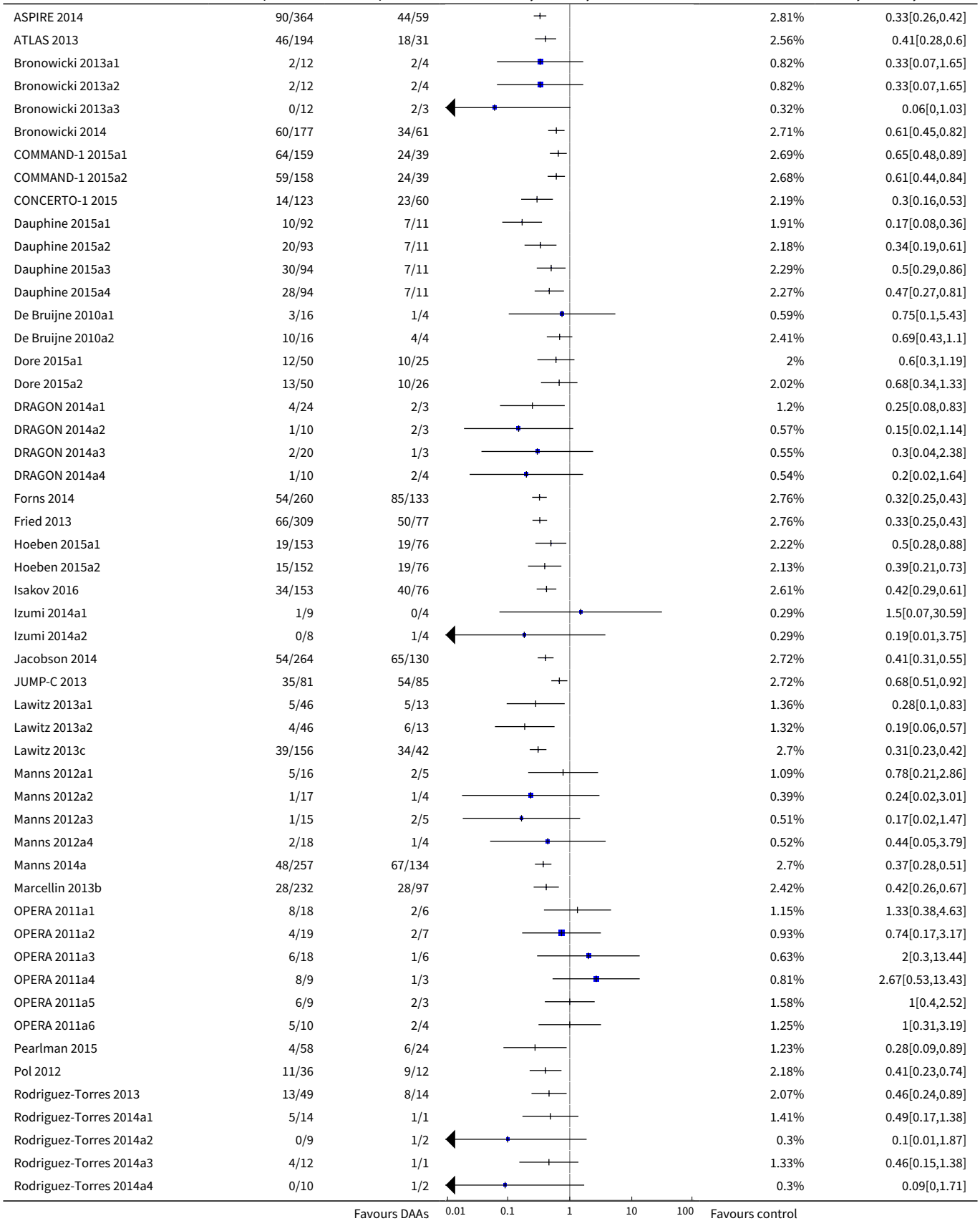
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.12.1 Treatment-naive					
ATLAS 2013	46/194	18/31		2.56%	0.41[0.28,0.6]
Bronowicki 2013a1	2/12	2/4		0.82%	0.33[0.07,1.65]
Bronowicki 2013a2	2/12	2/4		0.82%	0.33[0.07,1.65]
Bronowicki 2013a3	0/12	2/3		0.32%	0.06[0,1.03]
Bronowicki 2014	60/177	34/61		2.71%	0.61[0.45,0.82]
COMMAND-1 2015a1	64/159	24/39		2.69%	0.65[0.48,0.89]
COMMAND-1 2015a2	59/158	24/39		2.68%	0.61[0.44,0.84]
CONCERTO-1 2015	14/123	23/60		2.19%	0.3[0.16,0.53]
Dauphine 2015a1	10/92	7/11		1.91%	0.17[0.08,0.36]
Dauphine 2015a2	20/93	7/11		2.18%	0.34[0.19,0.61]
Dauphine 2015a3	30/94	7/11		2.29%	0.5[0.29,0.86]
Dauphine 2015a4	28/94	7/11		2.27%	0.47[0.27,0.81]
De Bruijne 2010a1	3/16	1/4		0.59%	0.75[0.1,5.43]
Dore 2015a1	12/50	10/25		2%	0.6[0.3,1.19]
Dore 2015a2	13/50	10/26		2.02%	0.68[0.34,1.33]
DRAGON 2014a1	4/24	2/3		1.2%	0.25[0.08,0.83]
DRAGON 2014a2	1/10	2/3		0.57%	0.15[0.02,1.14]
DRAGON 2014a3	2/20	1/3		0.55%	0.3[0.04,2.38]
DRAGON 2014a4	1/10	2/4		0.54%	0.2[0.02,1.64]
Fried 2013	66/309	50/77		2.76%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.22%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		2.13%	0.39[0.21,0.73]
Izumi 2014a1	1/9	0/4		0.29%	1.5[0.07,30.59]
Izumi 2014a2	0/8	1/4		0.29%	0.19[0.01,3.75]
Jacobson 2014	54/264	65/130		2.72%	0.41[0.31,0.55]
JUMP-C 2013	35/81	54/85		2.72%	0.68[0.51,0.92]
Lawitz 2013a1	5/46	5/13		1.36%	0.28[0.1,0.83]
Lawitz 2013a2	4/46	6/13		1.32%	0.19[0.06,0.57]
Manns 2012a1	5/16	2/5		1.09%	0.78[0.21,2.86]
Manns 2012a2	1/17	1/4		0.39%	0.24[0.02,3.01]
Manns 2012a3	1/15	2/5		0.51%	0.17[0.02,1.47]
Manns 2012a4	2/18	1/4		0.52%	0.44[0.05,3.79]
Manns 2014a	48/257	67/134		2.7%	0.37[0.28,0.51]
Marcellin 2013b	28/232	28/97		2.42%	0.42[0.26,0.67]
Muir 2014	8/20	10/10		2.29%	0.42[0.25,0.72]
OPERA 2011a1	8/18	2/6		1.15%	1.33[0.38,4.63]
OPERA 2011a2	4/19	2/7		0.93%	0.74[0.17,3.17]
OPERA 2011a3	6/18	1/6		0.63%	2[0.3,13.44]
Rodriguez-Torres 2013	13/49	8/14		2.07%	0.46[0.24,0.89]
Sullivan 2012	14/28	7/9		2.34%	0.64[0.39,1.07]
Tanwandee 2012	1/15	2/8		0.48%	0.27[0.03,2.51]
Tatum 2015a1	4/13	4/7		1.41%	0.54[0.19,1.52]
Tatum 2015a2	8/13	4/6		1.95%	0.92[0.45,1.88]
Wedemeyer 2013	183/324	39/84		2.79%	1.22[0.95,1.56]
Subtotal (95% CI)	**3540**	**1237**		**70.39%**	**0.48[0.41,0.56]**
Total events: 904 (DAAs), 584 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=111.04, df=43(P<0.0001); I^2=61.27%					
Test for overall effect: Z=8.99(P<0.0001)					

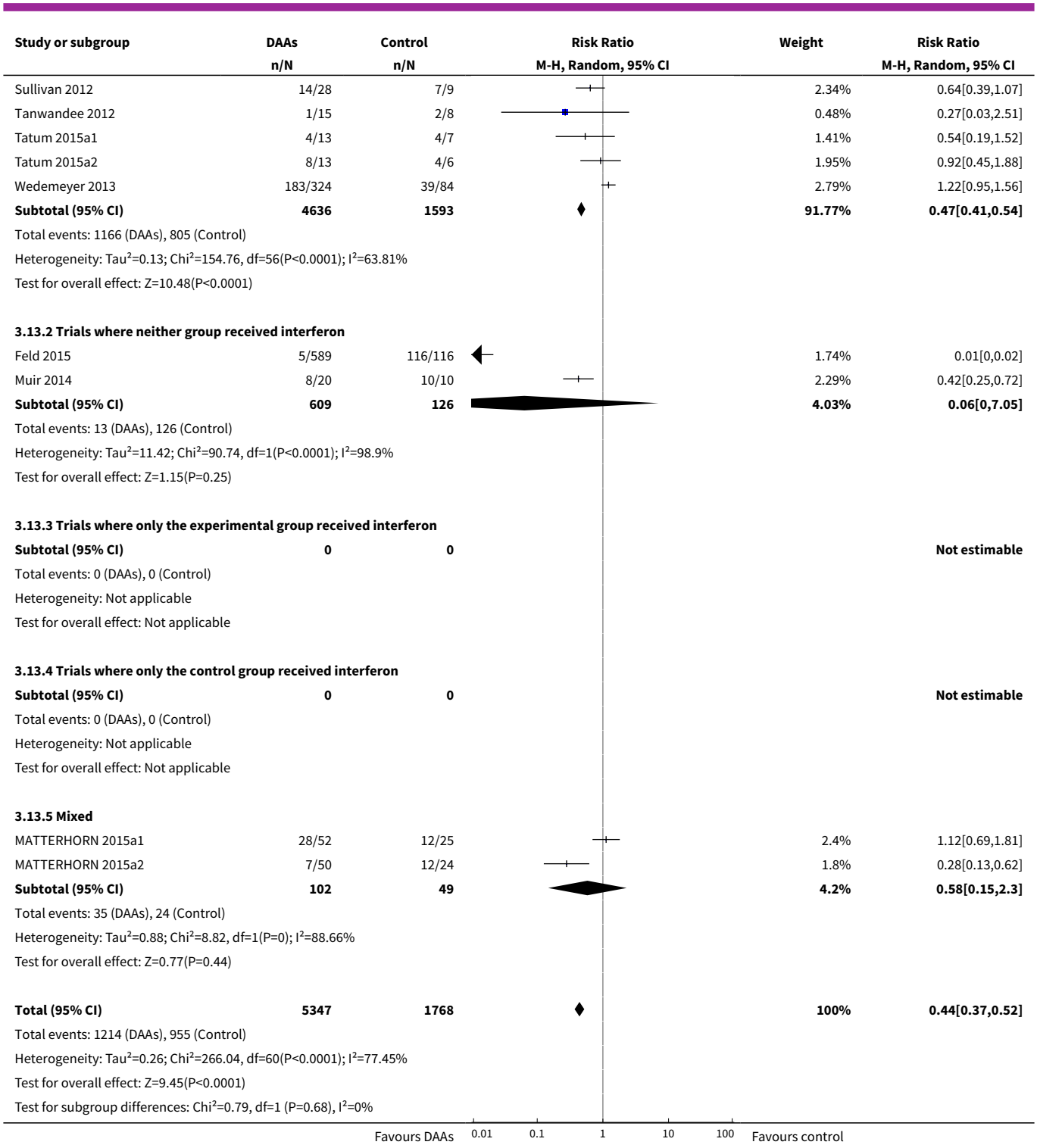




Analysis 3.13. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 13 Without sustained virological response - according to interferon.

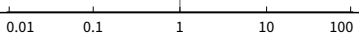






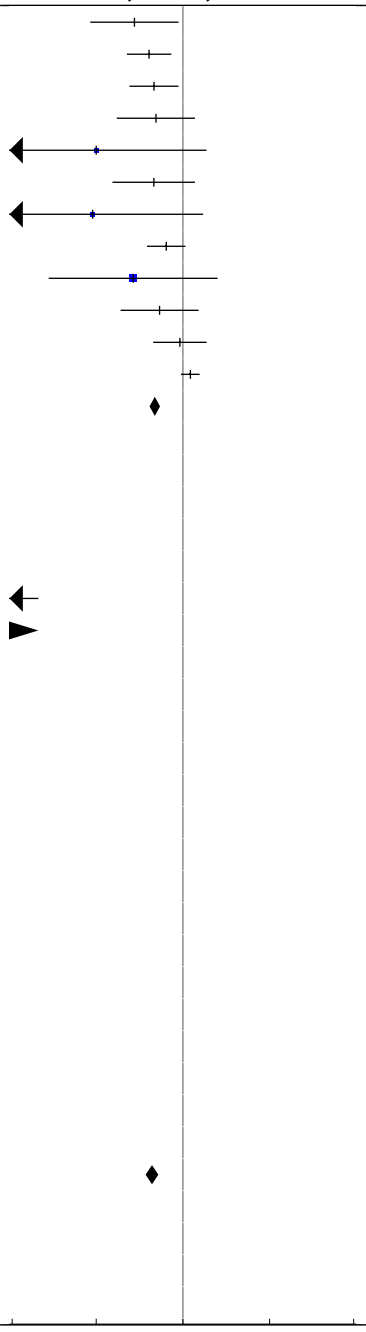
Analysis 3.14. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 14 Without sustained virological response - according to ribavirin.

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.14.1 Trials where both groups received ribavirin					
ASPIRE 2014	90/364	44/59		2.81%	0.33[0.26,0.42]
ATLAS 2013	46/194	18/31		2.56%	0.41[0.28,0.6]
Bronowicki 2013a1	2/12	2/4		0.82%	0.33[0.07,1.65]
Bronowicki 2013a2	2/12	2/4		0.82%	0.33[0.07,1.65]
Bronowicki 2013a3	0/12	2/3		0.32%	0.06[0,1.03]
Bronowicki 2014	60/177	34/61		2.71%	0.61[0.45,0.82]
COMMAND-1 2015a1	64/159	24/39		2.69%	0.65[0.48,0.89]
COMMAND-1 2015a2	59/158	24/39		2.68%	0.61[0.44,0.84]
CONCERTO-1 2015	14/123	23/60		2.19%	0.3[0.16,0.53]
Dauphine 2015a1	10/92	7/11		1.91%	0.17[0.08,0.36]
Dauphine 2015a2	20/93	7/11		2.18%	0.34[0.19,0.61]
Dauphine 2015a3	30/94	7/11		2.29%	0.5[0.29,0.86]
Dauphine 2015a4	28/94	7/11		2.27%	0.47[0.27,0.81]
De Bruijne 2010a1	3/16	1/4		0.59%	0.75[0.1,5.43]
De Bruijne 2010a2	10/16	4/4		2.41%	0.69[0.43,1.1]
Dore 2015a1	12/50	10/25		2%	0.6[0.3,1.19]
Dore 2015a2	13/50	10/26		2.02%	0.68[0.34,1.33]
DRAGON 2014a1	4/24	2/3		1.2%	0.25[0.08,0.83]
DRAGON 2014a2	1/10	2/3		0.57%	0.15[0.02,1.14]
DRAGON 2014a3	2/20	1/3		0.55%	0.3[0.04,2.38]
DRAGON 2014a4	1/10	2/4		0.54%	0.2[0.02,1.64]
Forns 2014	54/260	85/133		2.76%	0.32[0.25,0.43]
Fried 2013	66/309	50/77		2.76%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.22%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		2.13%	0.39[0.21,0.73]
Isakov 2016	34/153	40/76		2.61%	0.42[0.29,0.61]
Izumi 2014a1	1/9	0/4		0.29%	1.5[0.07,30.59]
Izumi 2014a2	0/8	1/4		0.29%	0.19[0.01,3.75]
Jacobson 2014	54/264	65/130		2.72%	0.41[0.31,0.55]
JUMP-C 2013	35/81	54/85		2.72%	0.68[0.51,0.92]
Lawitz 2013a1	5/46	5/13		1.36%	0.28[0.1,0.83]
Lawitz 2013a2	4/46	6/13		1.32%	0.19[0.06,0.57]
Lawitz 2013c	39/156	34/42		2.7%	0.31[0.23,0.42]
Manns 2012a1	5/16	2/5		1.09%	0.78[0.21,2.86]
Manns 2012a2	1/17	1/4		0.39%	0.24[0.02,3.01]
Manns 2012a3	1/15	2/5		0.51%	0.17[0.02,1.47]
Manns 2012a4	2/18	1/4		0.52%	0.44[0.05,3.79]
Manns 2014a	48/257	67/134		2.7%	0.37[0.28,0.51]
Marcellin 2013b	28/232	28/97		2.42%	0.42[0.26,0.67]
MATTERHORN 2015a1	28/52	12/25		2.4%	1.12[0.69,1.81]
MATTERHORN 2015a2	7/50	12/24		1.8%	0.28[0.13,0.62]
Muir 2014	8/20	10/10		2.29%	0.42[0.25,0.72]
OPERA 2011a1	8/18	2/6		1.15%	1.33[0.38,4.63]
OPERA 2011a2	4/19	2/7		0.93%	0.74[0.17,3.17]
OPERA 2011a3	6/18	1/6		0.63%	2[0.3,13.44]
OPERA 2011a4	8/9	1/3		0.81%	2.67[0.53,13.43]
OPERA 2011a5	6/9	2/3		1.58%	1[0.4,2.52]
OPERA 2011a6	5/10	2/4		1.25%	1[0.31,3.19]



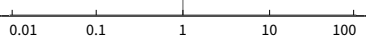
Favours DAAs — Favours control

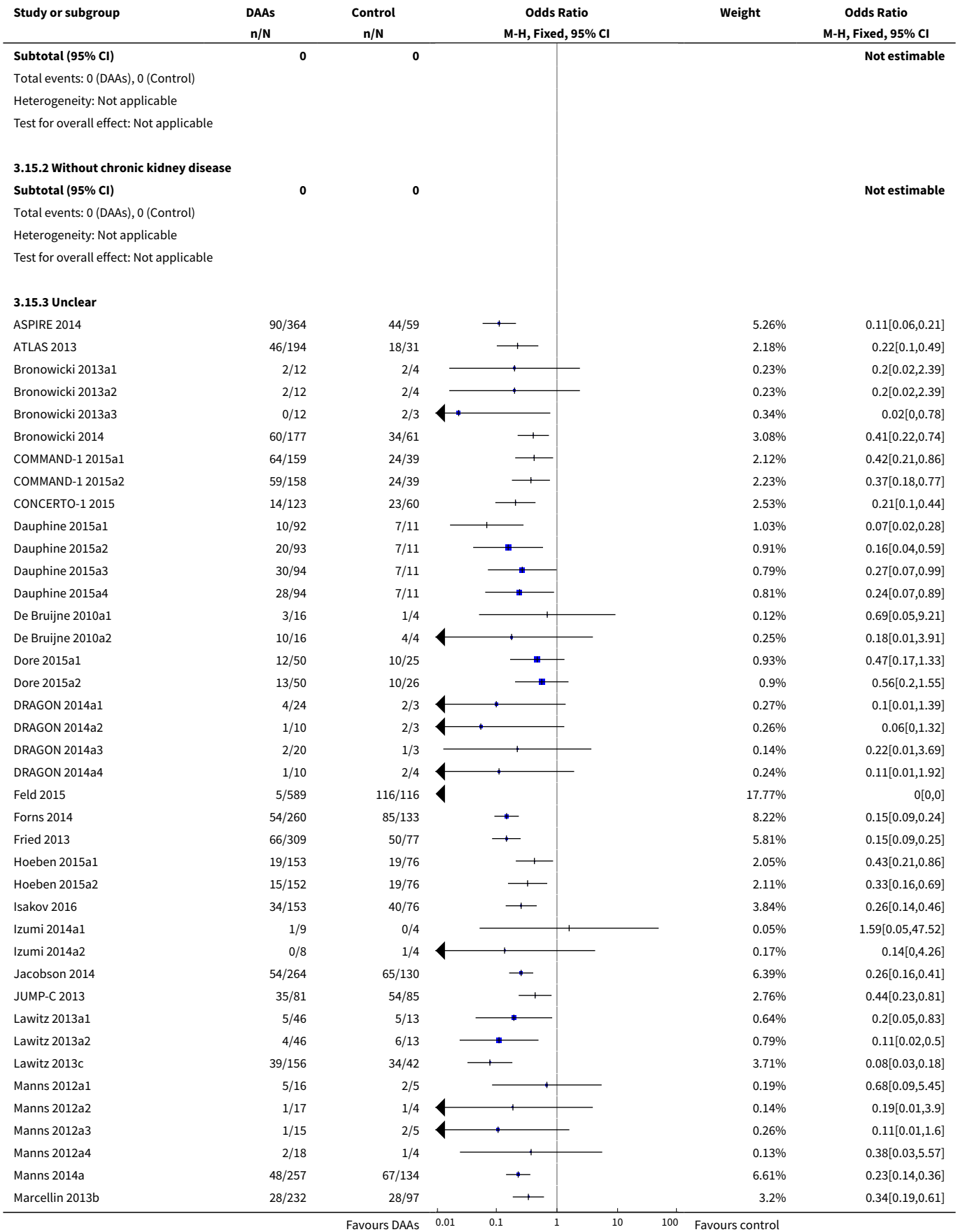
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pearlman 2015	4/58	6/24		1.23%	0.28[0.09,0.89]
Pol 2012	11/36	9/12		2.18%	0.41[0.23,0.74]
Rodriguez-Torres 2013	13/49	8/14		2.07%	0.46[0.24,0.89]
Rodriguez-Torres 2014a1	5/14	1/1		1.41%	0.49[0.17,1.38]
Rodriguez-Torres 2014a2	0/9	1/2		0.3%	0.1[0.01,1.87]
Rodriguez-Torres 2014a3	4/12	1/1		1.33%	0.46[0.15,1.38]
Rodriguez-Torres 2014a4	0/10	1/2		0.3%	0.09[0,1.71]
Sullivan 2012	14/28	7/9		2.34%	0.64[0.39,1.07]
Tanwandee 2012	1/15	2/8		0.48%	0.27[0.03,2.51]
Tatum 2015a1	4/13	4/7		1.41%	0.54[0.19,1.52]
Tatum 2015a2	8/13	4/6		1.95%	0.92[0.45,1.88]
Wedemeyer 2013	183/324	39/84		2.79%	1.22[0.95,1.56]
Subtotal (95% CI)	**4758**	**1652**		**98.26%**	**0.47[0.41,0.55]**
Total events: 1209 (DAAs), 839 (Control)					
Heterogeneity: Tau²=0.14; Chi²=168.88, df=59(P<0.0001); I²=65.06%					
Test for overall effect: Z=10.49(P<0.0001)					
3.14.2 Trials where neither group received ribavirin					
Feld 2015	5/589	116/116		1.74%	0.01[0,0.02]
Subtotal (95% CI)	**589**	**116**		**1.74%**	**0.01[0,0.02]**
Total events: 5 (DAAs), 116 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=11(P<0.0001)					
3.14.3 Trials where only the experimental group received ribavirin					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.14.4 Trials where only the control group received ribavirin					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**5347**	**1768**		**100%**	**0.44[0.37,0.52]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau²=0.26; Chi²=266.04, df=60(P<0.0001); I²=77.45%					
Test for overall effect: Z=9.45(P<0.0001)					
Test for subgroup differences: Chi²=83.17, df=1 (P<0.0001), I²=98.8%					



Analysis 3.15. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 15 Without sustained virological response - according to chronic kidney disease.

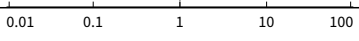
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.15.1 With chronic kidney disease					





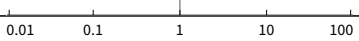
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.15.2 Without chronic kidney disease					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.15.3 Unclear					
ASPIRE 2014	90/364	44/59		5.26%	0.11[0.06,0.21]
ATLAS 2013	46/194	18/31		2.18%	0.22[0.1,0.49]
Bronowicki 2013a1	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a2	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a3	0/12	2/3		0.34%	0.02[0,0.78]
Bronowicki 2014	60/177	34/61		3.08%	0.41[0.22,0.74]
COMMAND-1 2015a1	64/159	24/39		2.12%	0.42[0.21,0.86]
COMMAND-1 2015a2	59/158	24/39		2.23%	0.37[0.18,0.77]
CONCERTO-1 2015	14/123	23/60		2.53%	0.21[0.1,0.44]
Dauphine 2015a1	10/92	7/11		1.03%	0.07[0.02,0.28]
Dauphine 2015a2	20/93	7/11		0.91%	0.16[0.04,0.59]
Dauphine 2015a3	30/94	7/11		0.79%	0.27[0.07,0.99]
Dauphine 2015a4	28/94	7/11		0.81%	0.24[0.07,0.89]
De Bruijne 2010a1	3/16	1/4		0.12%	0.69[0.05,9.21]
De Bruijne 2010a2	10/16	4/4		0.25%	0.18[0.01,3.91]
Dore 2015a1	12/50	10/25		0.93%	0.47[0.17,1.33]
Dore 2015a2	13/50	10/26		0.9%	0.56[0.2,1.55]
DRAGON 2014a1	4/24	2/3		0.27%	0.1[0.01,1.39]
DRAGON 2014a2	1/10	2/3		0.26%	0.06[0,1.32]
DRAGON 2014a3	2/20	1/3		0.14%	0.22[0.01,3.69]
DRAGON 2014a4	1/10	2/4		0.24%	0.11[0.01,1.92]
Feld 2015	5/589	116/116		17.77%	0[0,0]
Forns 2014	54/260	85/133		8.22%	0.15[0.09,0.24]
Fried 2013	66/309	50/77		5.81%	0.15[0.09,0.25]
Hoeben 2015a1	19/153	19/76		2.05%	0.43[0.21,0.86]
Hoeben 2015a2	15/152	19/76		2.11%	0.33[0.16,0.69]
Isakov 2016	34/153	40/76		3.84%	0.26[0.14,0.46]
Izumi 2014a1	1/9	0/4		0.05%	1.59[0.05,47.52]
Izumi 2014a2	0/8	1/4		0.17%	0.14[0,4.26]
Jacobson 2014	54/264	65/130		6.39%	0.26[0.16,0.41]
JUMP-C 2013	35/81	54/85		2.76%	0.44[0.23,0.81]
Lawitz 2013a1	5/46	5/13		0.64%	0.2[0.05,0.83]
Lawitz 2013a2	4/46	6/13		0.79%	0.11[0.02,0.5]
Lawitz 2013c	39/156	34/42		3.71%	0.08[0.03,0.18]
Manns 2012a1	5/16	2/5		0.19%	0.68[0.09,5.45]
Manns 2012a2	1/17	1/4		0.14%	0.19[0.01,3.9]
Manns 2012a3	1/15	2/5		0.26%	0.11[0.01,1.6]
Manns 2012a4	2/18	1/4		0.13%	0.38[0.03,5.57]
Manns 2014a	48/257	67/134		6.61%	0.23[0.14,0.36]
Marcellin 2013b	28/232	28/97		3.2%	0.34[0.19,0.61]

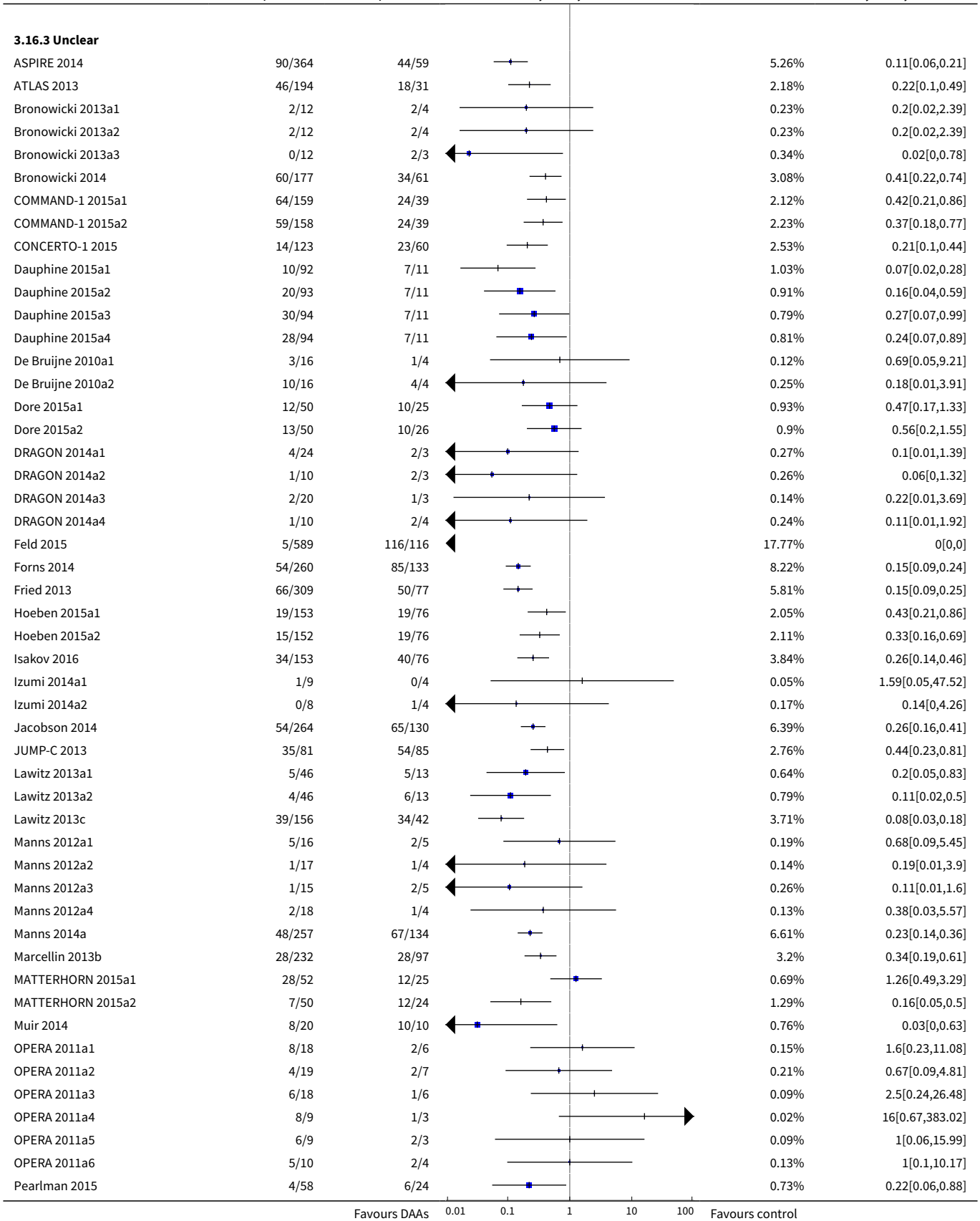
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
MATTERHORN 2015a1	28/52	12/25		0.69%	1.26[0.49,3.29]
MATTERHORN 2015a2	7/50	12/24		1.29%	0.16[0.05,0.5]
Muir 2014	8/20	10/10		0.76%	0.03[0,0.63]
OPERA 2011a1	8/18	2/6		0.15%	1.6[0.23,11.08]
OPERA 2011a2	4/19	2/7		0.21%	0.67[0.09,4.81]
OPERA 2011a3	6/18	1/6		0.09%	2.5[0.24,26.48]
OPERA 2011a4	8/9	1/3		0.02%	16[0.67,383.02]
OPERA 2011a5	6/9	2/3		0.09%	1[0.06,15.99]
OPERA 2011a6	5/10	2/4		0.13%	1[0.1,10.17]
Pearlman 2015	4/58	6/24		0.73%	0.22[0.06,0.88]
Pol 2012	11/36	9/12		0.86%	0.15[0.03,0.65]
Rodriguez-Torres 2013	13/49	8/14		0.84%	0.27[0.08,0.93]
Rodriguez-Torres 2014a1	5/14	1/1		0.15%	0.19[0.01,5.6]
Rodriguez-Torres 2014a2	0/9	1/2		0.2%	0.05[0,1.99]
Rodriguez-Torres 2014a3	4/12	1/1		0.16%	0.18[0.01,5.28]
Rodriguez-Torres 2014a4	0/10	1/2		0.21%	0.05[0,1.79]
Sullivan 2012	14/28	7/9		0.49%	0.29[0.05,1.62]
Tanwandee 2012	1/15	2/8		0.22%	0.21[0.02,2.84]
Tatum 2015a1	4/13	4/7		0.33%	0.33[0.05,2.24]
Tatum 2015a2	8/13	4/6		0.19%	0.8[0.1,6.1]
Wedemeyer 2013	183/324	39/84		2.49%	1.5[0.93,2.42]
Subtotal (95% CI)	**5347**	**1768**		**100%**	**0.24[0.22,0.27]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau^2=0; Chi^2=174.15, df=60(P<0.0001); I^2=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
Total (95% CI)	**5347**	**1768**		**100%**	**0.24[0.22,0.27]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau^2=0; Chi^2=174.15, df=60(P<0.0001); I^2=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
Test for subgroup differences: Not applicable					



Analysis 3.16. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 16 Without sustained virological response - according to cryoglobulinaemia.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.16.1 With cryoglobulinaemia					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.16.2 Without cryoglobulinaemia					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					





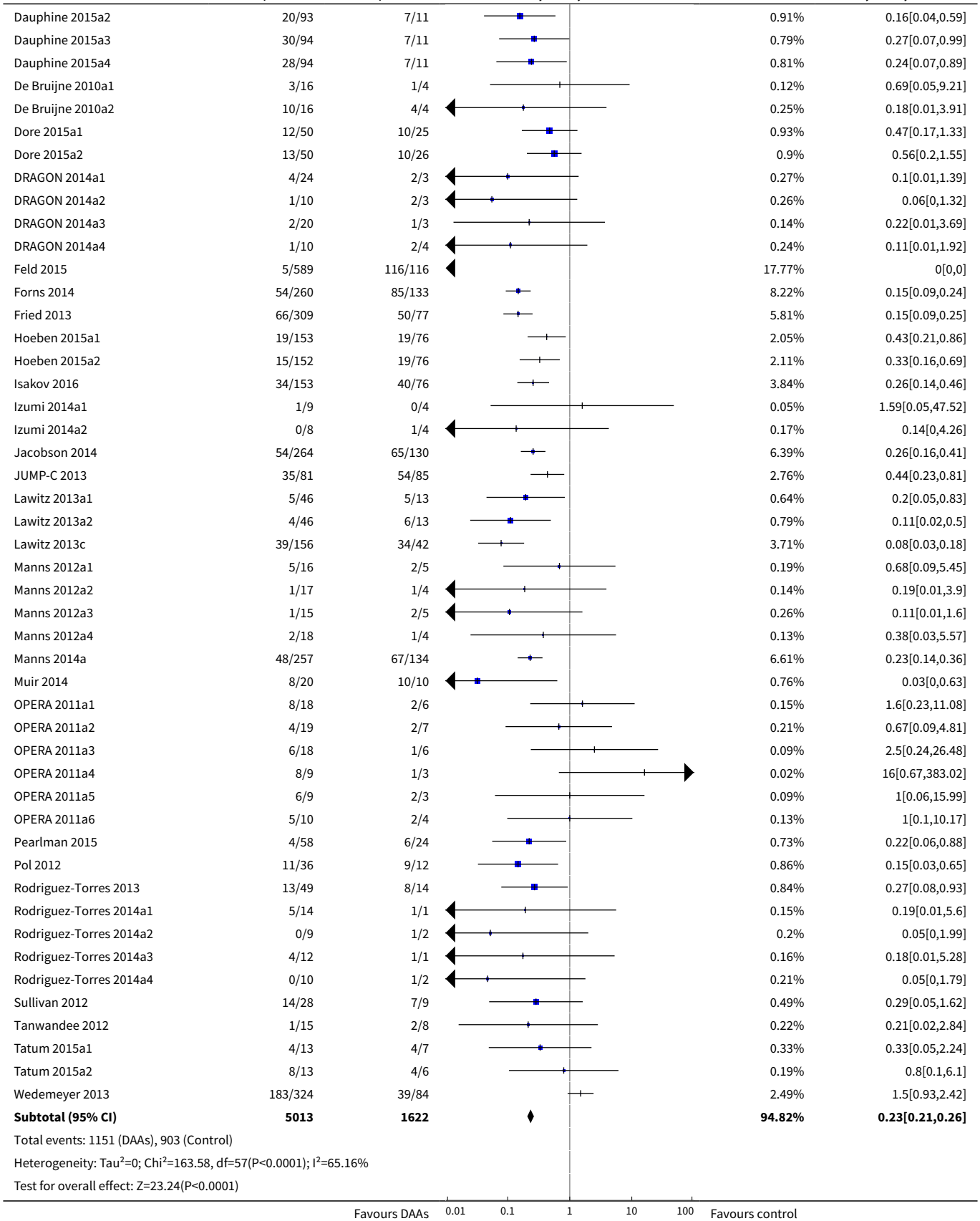
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Pol 2012	11/36	9/12		0.86%	0.15[0.03,0.65]
Rodriguez-Torres 2013	13/49	8/14		0.84%	0.27[0.08,0.93]
Rodriguez-Torres 2014a1	5/14	1/1		0.15%	0.19[0.01,5.6]
Rodriguez-Torres 2014a2	0/9	1/2		0.2%	0.05[0,1.99]
Rodriguez-Torres 2014a3	4/12	1/1		0.16%	0.18[0.01,5.28]
Rodriguez-Torres 2014a4	0/10	1/2		0.21%	0.05[0,1.79]
Sullivan 2012	14/28	7/9		0.49%	0.29[0.05,1.62]
Tanwandee 2012	1/15	2/8		0.22%	0.21[0.02,2.84]
Tatum 2015a1	4/13	4/7		0.33%	0.33[0.05,2.24]
Tatum 2015a2	8/13	4/6		0.19%	0.8[0.1,6.1]
Wedemeyer 2013	183/324	39/84		2.49%	1.5[0.93,2.42]
Subtotal (95% CI)	**5347**	**1768**		**100%**	**0.24[0.22,0.27]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau^2=0; Chi^2=174.15, df=60(P<0.0001); I^2=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
Total (95% CI)	**5347**	**1768**		**100%**	**0.24[0.22,0.27]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau^2=0; Chi^2=174.15, df=60(P<0.0001); I^2=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
Test for subgroup differences: Not applicable					

Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 3.17. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 17 Without sustained virological response - according to DAA group as co-intervention.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.17.1 Trials where DAA were used as co-intervention					
Marcellin 2013b	28/232	28/97		3.2%	0.34[0.19,0.61]
MATTERHORN 2015a1	28/52	12/25		0.69%	1.26[0.49,3.29]
MATTERHORN 2015a2	7/50	12/24		1.29%	0.16[0.05,0.5]
Subtotal (95% CI)	**334**	**146**		**5.18%**	**0.42[0.27,0.66]**
Total events: 63 (DAAs), 52 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.32, df=2(P=0.02); I^2=75.95%					
Test for overall effect: Z=3.79(P=0)					
3.17.2 Trials where DAA were not a co-intervention					
ASPIRE 2014	90/364	44/59		5.26%	0.11[0.06,0.21]
ATLAS 2013	46/194	18/31		2.18%	0.22[0.1,0.49]
Bronowicki 2013a1	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a2	2/12	2/4		0.23%	0.2[0.02,2.39]
Bronowicki 2013a3	0/12	2/3		0.34%	0.02[0,0.78]
Bronowicki 2014	60/177	34/61		3.08%	0.41[0.22,0.74]
COMMAND-1 2015a1	64/159	24/39		2.12%	0.42[0.21,0.86]
COMMAND-1 2015a2	59/158	24/39		2.23%	0.37[0.18,0.77]
CONCERTO-1 2015	14/123	23/60		2.53%	0.21[0.1,0.44]
Dauphine 2015a1	10/92	7/11		1.03%	0.07[0.02,0.28]

Favours DAAs 0.01 0.1 1 10 100 Favours control



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)	**5347**	**1768**	♦	**100%**	**0.24[0.22,0.27]**
Total events: 1214 (DAAs), 955 (Control)					
Heterogeneity: Tau^2=0; Chi^2=174.15, df=60(P<0.0001); I^2=65.55%					
Test for overall effect: Z=23.47(P<0.0001)					
Test for subgroup differences: Chi^2=5.9, df=1 (P=0.02), I^2=83.05%					

Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 3.18. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 18 Without sustained virological response - 'Best-worst case' scenario.

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ASPIRE 2014	90/396	51/66		2.7%	0.29[0.24,0.37]
ATLAS 2013	46/203	21/34		2.51%	0.37[0.25,0.53]
Bronowicki 2013a1	2/12	2/4		0.83%	0.33[0.07,1.65]
Bronowicki 2013a2	2/12	2/4		0.83%	0.33[0.07,1.65]
Bronowicki 2013a3	0/12	3/4		0.34%	0.05[0,0.88]
Bronowicki 2014	60/177	34/61		2.61%	0.61[0.45,0.82]
COMMAND-1 2015a1	64/159	24/39		2.59%	0.65[0.48,0.89]
COMMAND-1 2015a2	59/158	24/39		2.58%	0.61[0.44,0.84]
CONCERTO-1 2015	14/126	25/62		2.15%	0.28[0.15,0.49]
Dauphine 2015a1	10/94	7/11		1.88%	0.17[0.08,0.35]
Dauphine 2015a2	20/93	7/11		2.13%	0.34[0.19,0.61]
Dauphine 2015a3	32/94	8/12		2.31%	0.51[0.31,0.83]
Dauphine 2015a4	29/94	8/12		2.29%	0.46[0.28,0.76]
De Bruijne 2010a1	3/16	1/4		0.61%	0.75[0.1,5.43]
De Bruijne 2010a2	10/17	4/4		2.32%	0.65[0.4,1.06]
Dore 2015a1	12/50	10/25		1.96%	0.6[0.3,1.19]
Dore 2015a2	13/51	10/26		1.98%	0.66[0.34,1.3]
DRAGON 2014a1	4/27	2/3		1.2%	0.22[0.07,0.74]
DRAGON 2014a2	1/13	2/3		0.58%	0.12[0.01,0.89]
DRAGON 2014a3	2/26	1/3		0.56%	0.23[0.03,1.85]
DRAGON 2014a4	1/13	2/4		0.54%	0.15[0.02,1.29]
Feld 2015	5/590	116/116		1.72%	0.01[0,0.02]
Forns 2014	54/260	85/133		2.65%	0.32[0.25,0.43]
Fried 2013	66/309	50/77		2.65%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.16%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		2.08%	0.39[0.21,0.73]
Isakov 2016	34/159	43/79		2.52%	0.39[0.27,0.56]
Izumi 2014a1	1/9	0/4		0.3%	1.5[0.07,30.59]
Izumi 2014a2	0/8	1/4		0.3%	0.19[0.01,3.75]
Jacobson 2014	54/264	65/130		2.62%	0.41[0.31,0.55]
JUMP-C 2013	35/83	54/85		2.61%	0.66[0.49,0.9]
Lawitz 2013a1	5/48	5/13		1.36%	0.27[0.09,0.8]
Lawitz 2013a2	4/48	6/13		1.32%	0.18[0.06,0.55]
Lawitz 2013c	39/169	34/42		2.59%	0.29[0.21,0.39]
Manns 2012a1	5/18	2/5		1.09%	0.69[0.19,2.57]
Manns 2012a2	1/20	2/5		0.51%	0.13[0.01,1.12]

Favours DAAs 0.01 0.1 1 10 100 Favours control

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Manns 2012a3	1/18	2/5		0.52%	0.14[0.02,1.24]
Manns 2012a4	2/19	2/5		0.77%	0.26[0.05,1.43]
Manns 2014a	48/257	67/134		2.6%	0.37[0.28,0.51]
Marcellin 2013b	28/234	48/117		2.45%	0.29[0.19,0.44]
MATTERHORN 2015a1	28/52	12/25		2.33%	1.12[0.69,1.81]
MATTERHORN 2015a2	7/50	13/25		1.8%	0.27[0.12,0.59]
Muir 2014	8/20	10/10		2.23%	0.42[0.25,0.72]
OPERA 2011a1	8/18	3/7		1.46%	1.04[0.38,2.82]
OPERA 2011a2	4/19	1/6		0.6%	1.26[0.17,9.24]
OPERA 2011a3	6/18	4/9		1.49%	0.75[0.28,2]
OPERA 2011a4	8/9	1/3		0.82%	2.67[0.53,13.43]
OPERA 2011a5	6/9	2/3		1.57%	1[0.4,2.52]
OPERA 2011a6	5/10	1/3		0.75%	1.5[0.27,8.34]
Pearlman 2015	4/62	13/31		1.41%	0.15[0.05,0.43]
Pol 2012	11/36	9/12		2.13%	0.41[0.23,0.74]
Rodriguez-Torres 2013	13/50	8/14		2.03%	0.46[0.24,0.87]
Rodriguez-Torres 2014a1	5/16	4/4		1.86%	0.36[0.17,0.76]
Rodriguez-Torres 2014a2	0/14	2/3		0.33%	0.05[0,0.9]
Rodriguez-Torres 2014a3	4/15	4/4		1.71%	0.31[0.14,0.72]
Rodriguez-Torres 2014a4	0/15	2/3		0.33%	0.05[0,0.85]
Sullivan 2012	14/28	7/9		2.28%	0.64[0.39,1.07]
Tanwandee 2012	1/16	2/8		0.49%	0.25[0.03,2.36]
Tatum 2015a1	4/13	4/7		1.41%	0.54[0.19,1.52]
Tatum 2015a2	8/13	4/6		1.92%	0.92[0.45,1.88]
Wedemeyer 2013	183/324	39/84		2.68%	1.22[0.95,1.56]
Total (95% CI)	**5468**	**1826**		**100%**	**0.41[0.34,0.49]**
Total events: 1217 (DAAs), 1013 (Control)					
Heterogeneity: Tau^2=0.28; Chi^2=291.97, df=60(P<0.0001); I^2=79.45%					
Test for overall effect: Z=10.06(P<0.0001)					

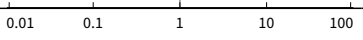
Analysis 3.19. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 19 Without sustained virological response - 'Worst-best case' scenario.

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ASPIRE 2014	122/396	44/66		2.79%	0.46[0.37,0.58]
ATLAS 2013	55/203	18/34		2.52%	0.51[0.35,0.76]
Bronowicki 2013a1	2/12	2/4		0.75%	0.33[0.07,1.65]
Bronowicki 2013a2	2/12	2/4		0.75%	0.33[0.07,1.65]
Bronowicki 2013a3	0/12	2/4		0.29%	0.08[0,1.34]
Bronowicki 2014	60/177	34/61		2.67%	0.61[0.45,0.82]
COMMAND-1 2015a1	64/159	24/39		2.66%	0.65[0.48,0.89]
COMMAND-1 2015a2	59/158	24/39		2.65%	0.61[0.44,0.84]
CONCERTO-1 2015	17/126	23/62		2.2%	0.36[0.21,0.63]
Dauphine 2015a1	12/94	7/11		1.91%	0.2[0.1,0.4]
Dauphine 2015a2	20/93	7/11		2.11%	0.34[0.19,0.61]
Dauphine 2015a3	32/94	7/12		2.19%	0.58[0.34,1.02]

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Dauphine 2015a4	29/94	7/12		2.16%	0.53[0.3,0.93]
De Bruijne 2010a1	3/16	1/4		0.54%	0.75[0.1,5.43]
De Bruijne 2010a2	11/17	4/4		2.39%	0.71[0.45,1.12]
Dore 2015a1	12/50	10/25		1.92%	0.6[0.3,1.19]
Dore 2015a2	14/51	10/26		1.97%	0.71[0.37,1.38]
DRAGON 2014a1	7/27	2/3		1.35%	0.39[0.14,1.08]
DRAGON 2014a2	4/13	2/3		1.19%	0.46[0.15,1.45]
DRAGON 2014a3	8/26	1/3		0.69%	0.92[0.17,5.06]
DRAGON 2014a4	4/13	2/4		1.03%	0.62[0.17,2.2]
Feld 2015	6/590	116/116		1.77%	0.01[0.01,0.02]
Forns 2014	54/260	85/133		2.73%	0.32[0.25,0.43]
Fried 2013	66/309	50/77		2.73%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.15%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		2.06%	0.39[0.21,0.73]
Isakov 2016	40/159	40/79		2.6%	0.5[0.35,0.7]
Izumi 2014a1	1/9	0/4		0.26%	1.5[0.07,30.59]
Izumi 2014a2	0/8	1/4		0.26%	0.19[0.01,3.75]
Jacobson 2014	54/264	65/130		2.69%	0.41[0.31,0.55]
JUMP-C 2013	37/83	54/85		2.7%	0.7[0.53,0.94]
Lawitz 2013a1	7/48	5/13		1.42%	0.38[0.14,1]
Lawitz 2013a2	6/48	6/13		1.45%	0.27[0.1,0.7]
Lawitz 2013c	52/169	34/42		2.73%	0.38[0.29,0.5]
Manns 2012a1	7/18	2/5		1.09%	0.97[0.29,3.29]
Manns 2012a2	4/20	1/5		0.55%	1[0.14,7.1]
Manns 2012a3	4/18	2/5		0.93%	0.56[0.14,2.2]
Manns 2012a4	3/19	1/5		0.51%	0.79[0.1,6.06]
Manns 2014a	48/257	67/134		2.67%	0.37[0.28,0.51]
Marcellin 2013b	30/234	28/117		2.37%	0.54[0.34,0.85]
MATTERHORN 2015a1	28/52	12/25		2.34%	1.12[0.69,1.81]
MATTERHORN 2015a2	7/50	12/25		1.71%	0.29[0.13,0.65]
Muir 2014	8/20	10/10		2.23%	0.42[0.25,0.72]
OPERA 2011a1	8/18	3/7		1.38%	1.04[0.38,2.82]
OPERA 2011a2	4/19	1/6		0.53%	1.26[0.17,9.24]
OPERA 2011a3	6/18	4/9		1.41%	0.75[0.28,2]
OPERA 2011a4	8/9	1/3		0.74%	2.67[0.53,13.43]
OPERA 2011a5	6/9	2/3		1.5%	1[0.4,2.52]
OPERA 2011a6	5/10	1/3		0.68%	1.5[0.27,8.34]
Pearlman 2015	8/62	6/31		1.43%	0.67[0.25,1.75]
Pol 2012	11/36	9/12		2.11%	0.41[0.23,0.74]
Rodriguez-Torres 2013	14/50	8/14		2.02%	0.49[0.26,0.92]
Rodriguez-Torres 2014a1	7/16	1/4		0.64%	1.75[0.29,10.44]
Rodriguez-Torres 2014a2	5/14	1/3		0.66%	1.07[0.19,6.15]
Rodriguez-Torres 2014a3	7/15	1/4		0.64%	1.87[0.31,11.09]
Rodriguez-Torres 2014a4	5/15	1/3		0.66%	1[0.17,5.77]
Sullivan 2012	14/28	7/9		2.28%	0.64[0.39,1.07]
Tanwandee 2012	2/16	2/8		0.65%	0.5[0.09,2.93]
Tatum 2015a1	4/13	4/7		1.33%	0.54[0.19,1.52]
Tatum 2015a2	8/13	4/6		1.87%	0.92[0.45,1.88]
Wedemeyer 2013	183/324	39/84		2.76%	1.22[0.95,1.56]
Total (95% CI)	**5468**	**1826**		**100%**	**0.51[0.43,0.6]**
Total events: 1338 (DAAs), 957 (Control)					

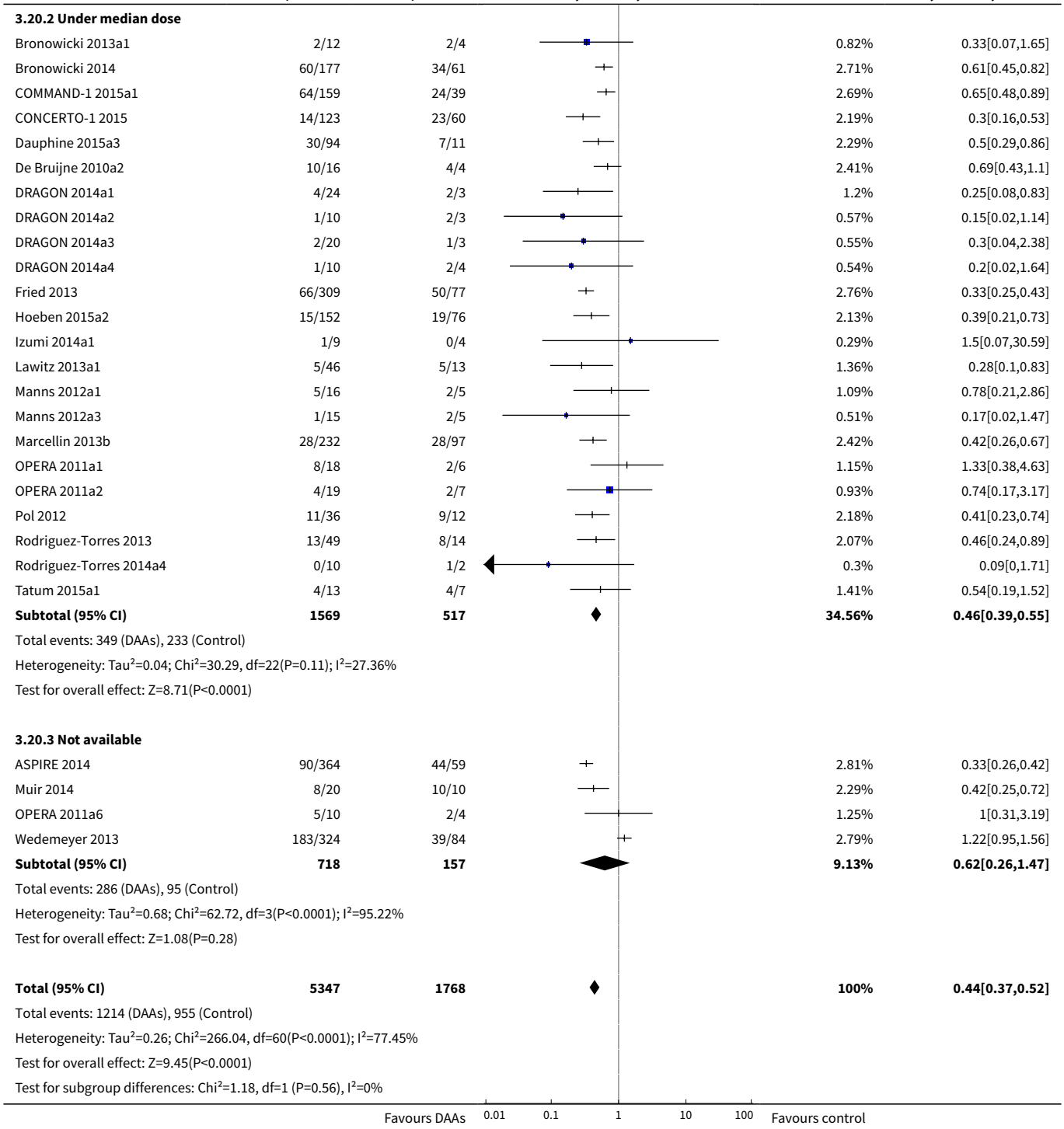
Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.23; Chi²=252.09, df=60(P<0.0001); I²=76.2%					
Test for overall effect: Z=8.2(P<0.0001)					



Analysis 3.20. Comparison 3 DAA on or on the way to the market versus placebo/no intervention (sustained virological response), Outcome 20 Without sustained virological response - according to median dose.

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.20.1 Over or equal to median dose					
ATLAS 2013	46/194	18/31		2.56%	0.41[0.28,0.6]
Bronowicki 2013a2	2/12	2/4		0.82%	0.33[0.07,1.65]
Bronowicki 2013a3	0/12	2/3		0.32%	0.06[0,1.03]
COMMAND-1 2015a2	59/158	24/39		2.68%	0.61[0.44,0.84]
Dauphine 2015a1	10/92	7/11		1.91%	0.17[0.08,0.36]
Dauphine 2015a2	20/93	7/11		2.18%	0.34[0.19,0.61]
Dauphine 2015a4	28/94	7/11		2.27%	0.47[0.27,0.81]
De Bruijne 2010a1	3/16	1/4		0.59%	0.75[0.1,5.43]
Dore 2015a1	12/50	10/25		2%	0.6[0.3,1.19]
Dore 2015a2	13/50	10/26		2.02%	0.68[0.34,1.33]
Feld 2015	5/589	116/116		1.74%	0.01[0,0.02]
Forns 2014	54/260	85/133		2.76%	0.32[0.25,0.43]
Hoeben 2015a1	19/153	19/76		2.22%	0.5[0.28,0.88]
Isakov 2016	34/153	40/76		2.61%	0.42[0.29,0.61]
Izumi 2014a2	0/8	1/4		0.29%	0.19[0.01,3.75]
Jacobson 2014	54/264	65/130		2.72%	0.41[0.31,0.55]
JUMP-C 2013	35/81	54/85		2.72%	0.68[0.51,0.92]
Lawitz 2013a2	4/46	6/13		1.32%	0.19[0.06,0.57]
Lawitz 2013c	39/156	34/42		2.7%	0.31[0.23,0.42]
Manns 2012a2	1/17	1/4		0.39%	0.24[0.02,3.01]
Manns 2012a4	2/18	1/4		0.52%	0.44[0.05,3.79]
Manns 2014a	48/257	67/134		2.7%	0.37[0.28,0.51]
MATTERHORN 2015a1	28/52	12/25		2.4%	1.12[0.69,1.81]
MATTERHORN 2015a2	7/50	12/24		1.8%	0.28[0.13,0.62]
OPERA 2011a3	6/18	1/6		0.63%	2[0.3,13.44]
OPERA 2011a4	8/9	1/3		0.81%	2.67[0.53,13.43]
OPERA 2011a5	6/9	2/3		1.58%	1[0.4,2.52]
Pearlman 2015	4/58	6/24		1.23%	0.28[0.09,0.89]
Rodriguez-Torres 2014a1	5/14	1/1		1.41%	0.49[0.17,1.38]
Rodriguez-Torres 2014a2	0/9	1/2		0.3%	0.1[0.01,1.87]
Rodriguez-Torres 2014a3	4/12	1/1		1.33%	0.46[0.15,1.38]
Sullivan 2012	14/28	7/9		2.34%	0.64[0.39,1.07]
Tanwandee 2012	1/15	2/8		0.48%	0.27[0.03,2.51]
Tatum 2015a2	8/13	4/6		1.95%	0.92[0.45,1.88]
Subtotal (95% CI)	**3060**	**1094**		**56.3%**	**0.41[0.32,0.53]**
Total events: 579 (DAAs), 627 (Control)					
Heterogeneity: Tau²=0.34; Chi²=173.3, df=33(P<0.0001); I²=80.96%					
Test for overall effect: Z=6.96(P<0.0001)					



Comparison 4. Danoprevir versus placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hepatitis C-related morbidity or all-cause mortality	9	781	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.06, 5.19]
2 Hepatitis C-related morbidity or all-cause mortality - according to dose	9	781	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.06, 5.19]
2.1 Over or equal to median dose	6	606	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.06, 5.19]
2.2 Under median dose	3	175	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Not available	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Serious adverse events	9		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Serious adverse events - according to median dose	9		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Over or equal to median dose	6		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Under median dose	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Not available	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Without sustained virological response	5	642	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.12, 0.32]
6 Without sustained virological response - according to median dose	5	642	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.12, 0.32]
6.1 Over or equal to median dose	4	537	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.11, 0.32]
6.2 Under median dose	1	105	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.07, 0.99]
6.3 Not available	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Danoprevir versus placebo/no intervention, Outcome 1 Hepatitis C-related morbidity or all-cause mortality.

Study or subgroup	Direct acting antivirals n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
ATLAS 2013	1/194	0/31		49.69%	0.49[0.02,12.26]
Dauphine 2015a1	0/92	0/11			Not estimable
Dauphine 2015a2	2/93	0/11		50.31%	0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11			Not estimable
Dauphine 2015a4	0/94	0/11			Not estimable
Forestier 2011a1	0/32	0/8			Not estimable
Forestier 2011a2	0/8	0/2			Not estimable
Forestier 2011b	0/47	0/12			Not estimable
Gane 2011	0/25	0/5			Not estimable
Total (95% CI)	**679**	**102**		**100%**	**0.56[0.06,5.19]**
Total events: 3 (Direct acting antivirals), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%					
Test for overall effect: Z=0.51(P=0.61)					

Analysis 4.2. Comparison 4 Danoprevir versus placebo/no intervention, Outcome 2 Hepatitis C-related morbidity or all-cause mortality - according to dose.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.2.1 Over or equal to median dose					
ATLAS 2013	1/194	0/31		49.69%	0.49[0.02,12.26]
Dauphine 2015a1	0/92	0/11			Not estimable
Dauphine 2015a2	2/93	0/11		50.31%	0.63[0.03,13.92]
Dauphine 2015a4	0/94	0/11			Not estimable
Forestier 2011a2	0/8	0/2			Not estimable
Forestier 2011b	0/47	0/12			Not estimable
Subtotal (95% CI)	**528**	**78**		**100%**	**0.56[0.06,5.19]**
Total events: 3 (DAA), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%					
Test for overall effect: Z=0.51(P=0.61)					
4.2.2 Under median dose					
Dauphine 2015a3	0/94	0/11			Not estimable
Forestier 2011a1	0/32	0/8			Not estimable
Gane 2011	0/25	0/5			Not estimable
Subtotal (95% CI)	**151**	**24**			**Not estimable**
Total events: 0 (DAA), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.2.3 Not available					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAA), 0 (Control)					
Heterogeneity: Not applicable					

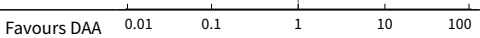
Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Test for overall effect: Not applicable					
Total (95% CI)	**679**	**102**		**100%**	**0.56[0.06,5.19]**
Total events: 3 (DAA), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%					
Test for overall effect: Z=0.51(P=0.61)					
Test for subgroup differences: Not applicable					

Analysis 4.3. Comparison 4 Danoprevir versus placebo/no intervention, Outcome 3 Serious adverse events.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Gane 2011	1/25	0/5		0.67[0.02,18.84]

Analysis 4.4. Comparison 4 Danoprevir versus placebo/no intervention, Outcome 4 Serious adverse events - according to median dose.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
4.4.1 Over or equal to median dose				
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
4.4.2 Under median dose				
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
4.4.3 Not available				



Analysis 4.5. Comparison 4 Danoprevir versus placebo/no intervention, Outcome 5 Without sustained virological response.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
ATLAS 2013	46/194	18/31		38.2%	0.22[0.1,0.49]
Dauphine 2015a1	10/92	7/11		17.98%	0.07[0.02,0.28]
Dauphine 2015a2	20/93	7/11		15.85%	0.16[0.04,0.59]
Dauphine 2015a3	30/94	7/11		13.77%	0.27[0.07,0.99]
Dauphine 2015a4	28/94	7/11		14.2%	0.24[0.07,0.89]
Total (95% CI)	**567**	**75**		**100%**	**0.19[0.12,0.32]**
Total events: 134 (DAA), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.66, df=4(P=0.62); I^2=0%					
Test for overall effect: Z=6.33(P<0.0001)					

Analysis 4.6. Comparison 4 Danoprevir versus placebo/no intervention, Outcome 6 Without sustained virological response - according to median dose.

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.6.1 Over or equal to median dose					
ATLAS 2013	46/194	18/31		38.2%	0.22[0.1,0.49]
Dauphine 2015a1	10/92	7/11		17.98%	0.07[0.02,0.28]
Dauphine 2015a2	20/93	7/11		15.85%	0.16[0.04,0.59]
Dauphine 2015a4	28/94	7/11		14.2%	0.24[0.07,0.89]
Subtotal (95% CI)	**473**	**64**		**86.23%**	**0.18[0.11,0.32]**
Total events: 104 (DAA), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.34, df=3(P=0.51); I^2=0%					
Test for overall effect: Z=6.06(P<0.0001)					
4.6.2 Under median dose					
Dauphine 2015a3	30/94	7/11		13.77%	0.27[0.07,0.99]
Subtotal (95% CI)	**94**	**11**		**13.77%**	**0.27[0.07,0.99]**
Total events: 30 (DAA), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.98(P=0.05)					
4.6.3 Not available					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAA), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**567**	**75**		**100%**	**0.19[0.12,0.32]**
Total events: 134 (DAA), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.66, df=4(P=0.62); I^2=0%					
Test for overall effect: Z=6.33(P<0.0001)					
Test for subgroup differences: Chi^2=0.28, df=1 (P=0.6), I^2=0%					

Comparison 5. All DAA versus placebo/no intervention/other medical intervention (morbidity or all-cause mortality analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hepatitis C-related morbidity or all-cause mortality	95		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Trials assessing DAAs on or on the way to the market	71		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Trials assessing DAAs withdrawn from market	22		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Trials using other medical intervention as control group	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Trials using other medical intervention as experimental group	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Hepatitis C-related morbidity or all-cause mortality - drugs not discontinued	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Trials assessing discontinued drugs	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Trials assessing drugs still used	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Hepatitis C-related morbidity or all-cause mortality - bias risk	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 Trials with a high risk of bias	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Trials with a low risk of bias	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Hepatitis C-related morbidity or all-cause mortality - according to type of DAA	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 ABT-072	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 ACH-2684	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Alisporivir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 ALS-2200	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 Asunaprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 Balapiravir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Beclabuvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.8 BILB-1941	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.9 BIT-225	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.10 Boceprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.11 Ciluprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.12 Daclatasvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.13 Danoprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.14 Dasabuvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.15 Deleobuvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.16 Faldaprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.17 Filibuvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.18 Grazoprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.19 GS-6620	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.20 GS-9256	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.21 GS-9451	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.22 GS-9669	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.23 GS-9851	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.24 GS-9857	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.25 GSK2336805	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.26 GSK2878175	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.27 IDX-184	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.28 INX-08189	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.29 Ledispasvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.30 Mericitabine	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.31 Narlaprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.32 Nesbuvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.33 Odalasavir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.34 Ombitasvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.35 Paritaprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.36 PHX1766	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.37 PPI-461	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.38 PSI-352938	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.39 Samatasvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.40 Setrobuvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.41 Simeprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.42 Sofosbuvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.43 Sovaprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.44 Tegobuvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.45 Telaprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.46 Valopicitabine	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.47 Vaniprevir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.48 VCH-759	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.49 VCH-916	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.50 Velpatasvir	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.51 VX-222	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.52 Mixed	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Hepatitis C-related morbidity or all-cause mortality - according to group of DAA	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.1 Cyclophilin	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 NS3/NS4A inhibitors	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 NS5B inhibitors (NPI)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 NS5B inhibitors (NNPI)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.5 NS5A inhibitors	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.6 VPU-ion channel inhibitors	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.7 Mixed	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Hepatitis C-related morbidity or all-cause mortality - according to HIV-infection	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 With HIV-infection	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Without HIV-infection	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Mixed (with and without HIV-infection)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Hepatitis C-related morbidity or all-cause mortality - according to comorbidity	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.1 With comorbidity	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Without comorbidity	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Hepatitis C-related morbidity or all-cause mortality - according to viral genotype	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.1 Genotype 1	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Genotype 2	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Genotype 3	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 Genotype 4	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.5 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Hepatitis C-related morbidity or all-cause mortality - according to human genotype (IL28b)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.1 IL28b (CC)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 IL28B (CT)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 IL28B (TT)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 IL28B (CT + TT)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.5 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Hepatitis C-related morbidity or all-cause mortality - according to Asian-region	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

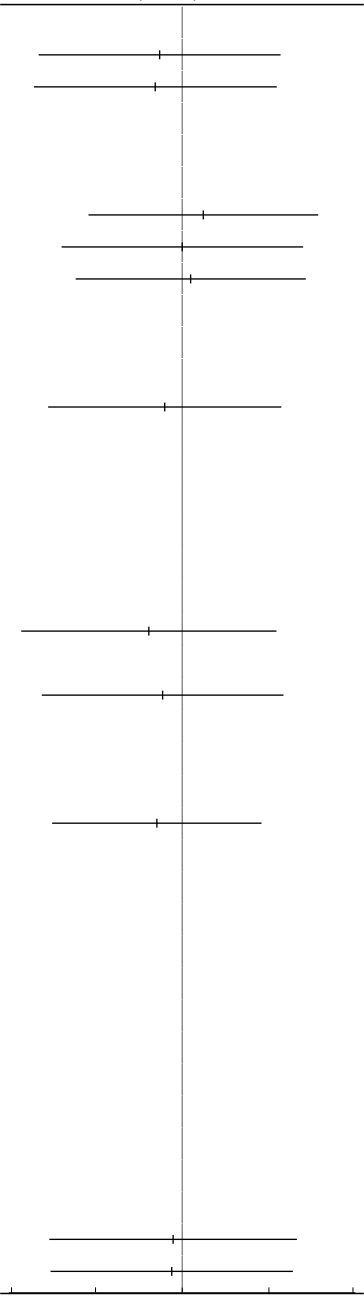
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 From Asian region	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Not from Asian region	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Mixed	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Hepatitis C-related morbidity or all-cause mortality - according to specific ethnicities	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.1 White	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Black	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Hispanic	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.4 Mixed	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.5 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Hepatitis C-related morbidity or all-cause mortality - according to reaching planned sample size	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.1 Trials reaching planned sample size	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Trials not reaching planned sample size	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Hepatitis C-related morbidity or all-cause mortality - according to prior treatment	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.1 Treatment-naive	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Treatment-experienced	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Mixed	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.4 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Hepatitis C-related morbidity or all-cause mortality - according to interferon	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.1 Trials where both groups received interferon	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.2 Trials where neither group received interferon	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Trials where only the experimental group received interferon	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.4 Trials where only the control group received interferon	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Hepatitis C-related morbidity or all-cause mortality - according to ribavirin	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.1 Trials where both groups received ribavirin	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Trials where neither group received ribavirin	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Trials where only the experimental group received ribavirin	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.4 Trials where only the control group received ribavirin	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Hepatitis C-related morbidity or all-cause mortality - according to chronic kidney disease	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.1 With chronic kidney disease	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Without chronic kidney disease	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Hepatitis C-related morbidity or all-cause mortality - according to cryoglobulinaemia	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.1 With cryoglobulinaemia	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Without cryoglobulinaemia	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 Unclear	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Hepatitis C-related morbidity or all-cause mortality - according to DAA group as co-intervention	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.1 Trials where DAA were used as co-intervention	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

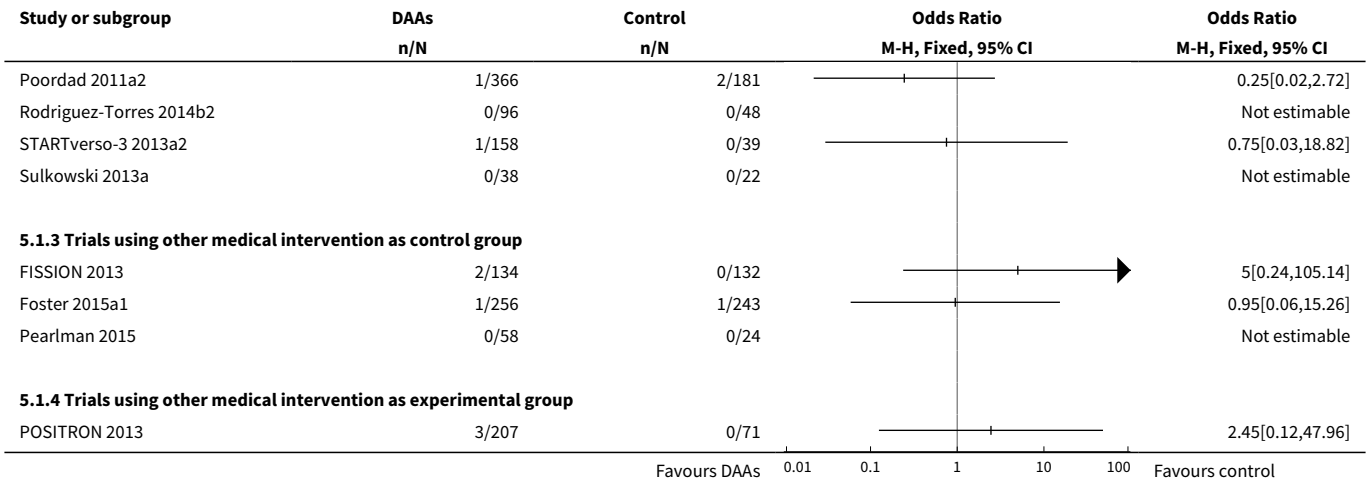
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.2 Trials where DAA were not a co-intervention	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 All DAA versus placebo/no intervention/other medical intervention (morbidity or all-cause mortality analyses), Outcome 1 Hepatitis C-related morbidity or all-cause mortality.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
5.1.1 Trials assessing DAAs on or on the way to the market				
ASPIRE 2014	1/364	0/66		0.55[0.02,13.62]
ATLAS 2013	1/194	0/31		0.49[0.02,12.26]
Bronowicki 2013a1	0/12	0/4		Not estimable
Bronowicki 2013a2	0/12	0/4		Not estimable
Bronowicki 2013a3	0/12	0/3		Not estimable
Bronowicki 2014	2/177	0/61		1.75[0.08,37.01]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	2/159	0/39		1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39		Not estimable
CONCERTO-1 2015	0/123	0/60		Not estimable
Dauphine 2015a1	0/92	0/11		Not estimable
Dauphine 2015a2	2/93	0/11		0.63[0.03,13.92]
Dauphine 2015a3	0/94	0/11		Not estimable
Dauphine 2015a4	0/94	0/11		Not estimable
Dore 2015a1	0/50	0/25		Not estimable
Dore 2015a2	0/50	0/25		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	0/13	0/3		Not estimable
DRAGON 2014a3	1/26	0/3		0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4		Not estimable
Feld 2015	1/589	0/116		0.59[0.02,14.67]
Forestier 2011a1	0/32	0/8		Not estimable
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	0/47	0/12		Not estimable
Forns 2014	1/260	1/133		0.51[0.03,8.21]
Fried 2013	0/309	0/77		Not estimable
Fundamental 2014a1	0/120	0/38		Not estimable
Fundamental 2014a2	0/115	0/38		Not estimable
Fundamental 2014a3	0/108	0/38		Not estimable
Gane 2010	0/57	0/14		Not estimable
Gane 2011	0/25	0/5		Not estimable
Gardner 2014a	0/11	0/4		Not estimable
HALLMARK-DUAL 2014	0/205	0/102		Not estimable
Izumi 2014a1	0/9	0/4		Not estimable
Izumi 2014a2	0/8	0/4		Not estimable
JUMP-C 2013	0/81	0/83		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	1/169	0/42		0.76[0.03,18.9]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	0/18	0/5		Not estimable
Manns 2012a2	0/20	0/5		Not estimable
Manns 2012a3	0/18	0/5		Not estimable
Manns 2012a4	0/19	0/4		Not estimable
MATTERHORN 2015a1	0/52	0/24		Not estimable
MATTERHORN 2015a2	0/50	0/25		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	0/18	0/4		Not estimable
OPERA 2011a2	0/19	0/3		Not estimable
OPERA 2011a3	0/18	0/6		Not estimable
OPERA 2011a4	0/9	0/4		Not estimable
OPERA 2011a5	0/8	0/3		Not estimable
OPERA 2011a6	0/10	0/3		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	0/36	0/12		Not estimable
Rodriguez-Torres 2014a1	0/16	0/4		Not estimable
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	0/15	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	0/13	0/7		Not estimable
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
5.1.2 Trials assessing DAAs withdrawn from market				
ADVANCE 2011a1	2/365	1/182		1[0.09,11.07]
ADVANCE 2011a2	1/365	0/183		1.51[0.06,37.26]
Bacon 2011a1	1/162	0/40		0.75[0.03,18.81]
Bacon 2011a2	1/161	0/40		0.76[0.03,18.93]
Benhamou 2013a1	0/8	0/4		Not estimable
Benhamou 2013a2	0/8	0/4		Not estimable
Cooper 2009	0/23	0/9		Not estimable
Forestier 2007	0/16	0/4		Not estimable
Forestier 2011a1	0/14	0/9		Not estimable
Forestier 2011a2	0/17	0/9		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Nelson 2012a1	0/74	1/12		0.05[0,1.34]
Nelson 2012a2	0/70	0/12		Not estimable
Nelson 2012a3	2/72	0/12		0.89[0.04,19.59]
Nelson 2012a4	1/71	0/12		0.53[0.02,13.81]
Nelson 2012a5	0/70	0/12		Not estimable
Nelson 2012a6	0/75	0/12		Not estimable
Poordad 2011a1	1/368	2/182		0.25[0.02,2.72]



Comparison 6. All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Trials assessing DAAs on or on the way to the market	101		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Trials assessing DAAs withdrawn from market	62		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Trials using other medical intervention as control group	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Trials using other medical intervention as experimental group	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Serious adverse events - bias risk	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Trials with a high risk of bias	167		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Trials with a low risk of bias	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Serious adverse events - according to type of DAA	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 ABT-072	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 ACH-2684	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Alisporivir	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 ALS-2200	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Asunaprevir	6		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 Balapiravir	9		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.7 Beclabuvir	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.8 BILB-1941	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.9 BIT-225	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.10 Boceprevir	13		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.11 Ciluprevir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.12 Daclatasvir	14		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.13 Danoprevir	9		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.14 Dasabuvir	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.15 Deleobuvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.16 Faldaprevir	13		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.17 Filibuvir	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.18 Grazoprevir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.19 GS-6620	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.20 GS-9256	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.21 GS-9451	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.22 GS-9669	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.23 GS-9851	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.24 GS-9857	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.25 GSK2336805	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.26 GSK2878175	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.27 IDX-184	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.28 INX-08189	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.29 Ledispasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.30 Mericitabine	7		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.31 Narlaprevir	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.32 Nesbuvir	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.33 Odalasavir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.34 Ombitasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.35 Paritaprevir	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.36 PHX1766	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.37 PPI-461	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.38 PSI-352938	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.39 Samatasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.40 Setrobuvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.41 Simeprevir	19		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.42 Sofosbuvir	6		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.43 Sovaprevir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.44 Tegobuvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.45 Telaprevir	13		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.46 Valopicitabine	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.47 Vaniprevir	10		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.48 VCH-759	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.49 VCH-916	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.50 Velpatasvir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.51 VX-222	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.52 Mixed	8		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Serious adverse events - according to group of DAA	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Cyclophilin	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 NS3/NS4A inhibitors	92		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 NS5B inhibitors (NPI)	24		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 NS5B inhibitors (NNPI)	14		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5 NS5A inhibitors	27		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 VPU-ion channel inhibitors	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Mixed	7		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Serious adverse events - according to HIV-infection	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 With HIV-infection	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Without HIV-infection	154		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Mixed (with and without HIV-infection)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Unclear	11		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Serious adverse events - according to comorbidity	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 With comorbidity	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Without comorbidity	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Unclear	167		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Serious adverse events - according to viral genotype	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Genotype 1	138		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Genotype 2	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Genotype 3	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Genotype 4	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.5 Mixed	26		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Serious adverse events - according to human genotype (IL28b)	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 IL28b (CC)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 IL28B (CT)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 IL28B (TT)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 IL28B (CT + TT)	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.5 Unclear	79		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

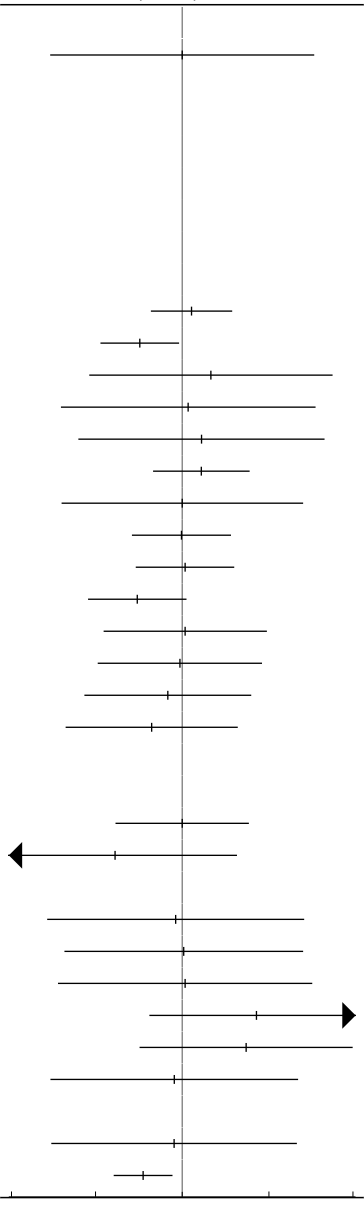
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.6 Mixed IL28b	88		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Serious adverse events - according to Asian-region	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 From Asian region	12		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Not from Asian region	119		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Mixed	31		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 Unclear	5		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Serious adverse events - according to specific ethnicities	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 White	3		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Black	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Hispanic	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 Mixed	133		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.5 Unclear	31		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Serious adverse events - according to reaching planned sample size	0		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Trials reaching planned sample size	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Trials not reaching planned sample size	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Unclear	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Serious adverse events - according to prior treatment	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 Treatment-naive	122		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Treatment-experienced	27		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Mixed	18		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.4 Unclear	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Serious adverse events - according to interferon	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Trials where both groups received interferon	126		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Trials where neither group received interferon	40		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Trials where only the experimental group received interferon	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.4 Trials where only the control group received interferon	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Serious adverse events - according to ribavirin	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 Trials where both groups received ribavirin	127		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Trials where neither group received ribavirin	37		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Trials where only the experimental group received ribavirin	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.4 Trials where only the control group received ribavirin	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Serious adverse events - according to chronic kidney disease	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 With chronic kidney disease	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Without chronic kidney disease	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Unclear	167		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Serious adverse events - according to cryoglobulinaemia	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.1 With cryoglobulinaemia	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Without cryoglobulinaemia	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Unclear	167		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Serious adverse events - according to DAA group as co-intervention	167		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

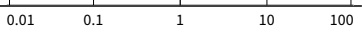
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Trials where DAA were used as co-intervention	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Trials where DAA were not a co-intervention	165		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 1 Serious adverse events.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.1.1 Trials assessing DAAs on or on the way to the market				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable

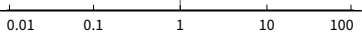


Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Sims 2014	0/20	0/4		Not estimable
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
6.1.2 Trials assessing DAAs withdrawn from market				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Erhardt 2009	0/77	0/19		Not estimable
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forestier 2007	0/8	0/4		Not estimable
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hinrichsen 2004	0/41	0/10		Not estimable
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2012	0/33	0/8		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Mallalieu 2014	0/27	0/8		Not estimable
Manns 2011	2/26	0/8		1.73[0.08,39.88]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]

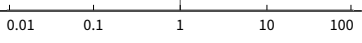
Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nishiguchi 2014a2	0/6	0/2		Not estimable
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
6.1.3 Trials using other medical intervention as control group				
FISSION 2013	2/134	0/132		5[0.24,105.14]
Foster 2015a1	1/256	1/243		0.95[0.06,15.26]
Pearlman 2015	0/58	0/24		Not estimable
6.1.4 Trials using other medical intervention as experimental group				
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]



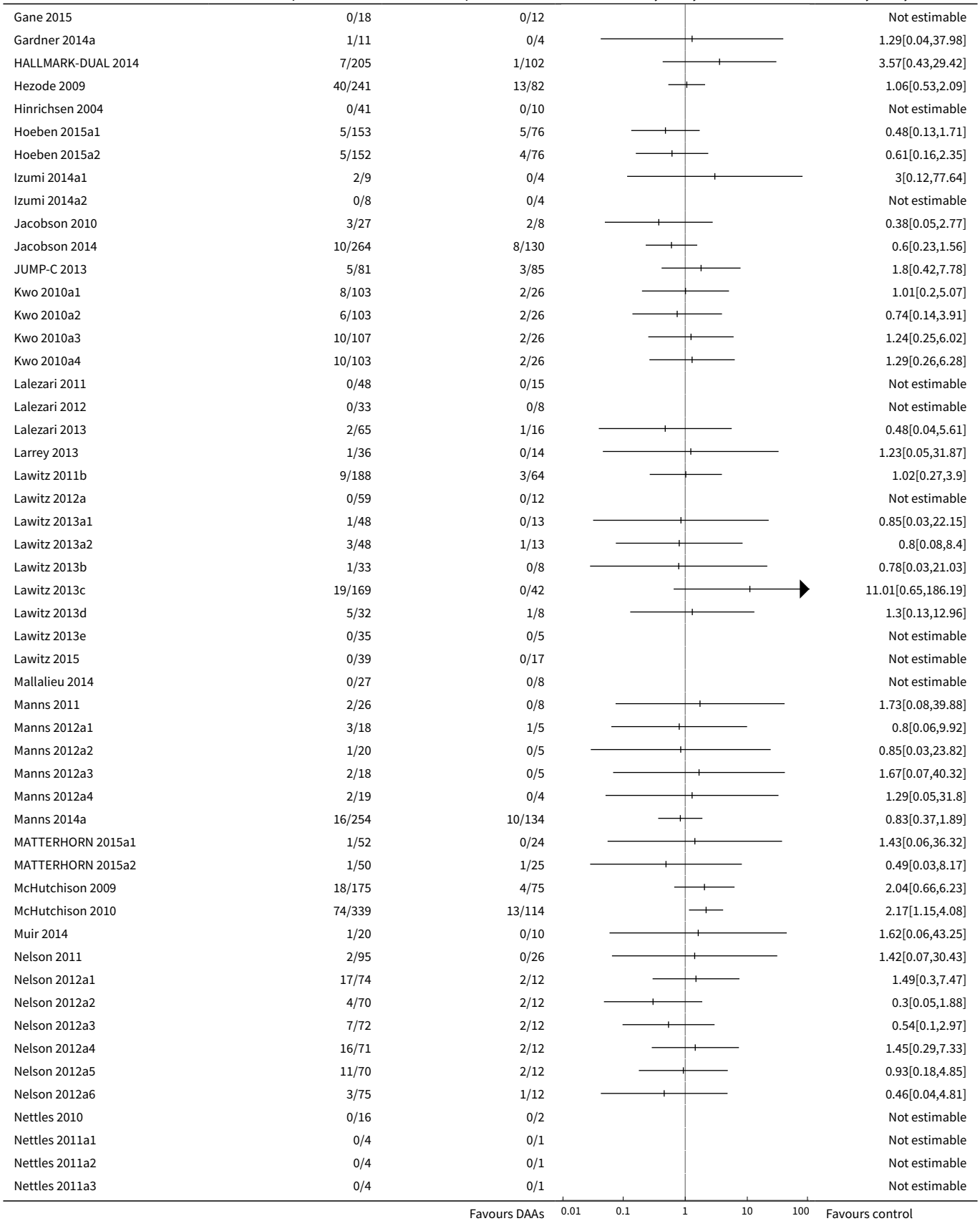
Analysis 6.2. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 2 Serious adverse events - bias risk.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.2.1 Trials with a high risk of bias				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forestier 2007	0/8	0/4		Not estimable
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]

Favours DAAs | Favours control

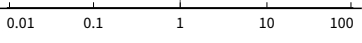


Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hinrichsen 2004	0/41	0/10		Not estimable
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2011	0/48	0/15		Not estimable
Lalezari 2012	0/33	0/8		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Manns 2011	2/26	0/8		1.73[0.08,39.88]
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Reddy 2007	0/32	0/8		Not estimable
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]

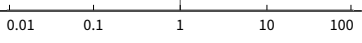
Favours DAAs Favours control

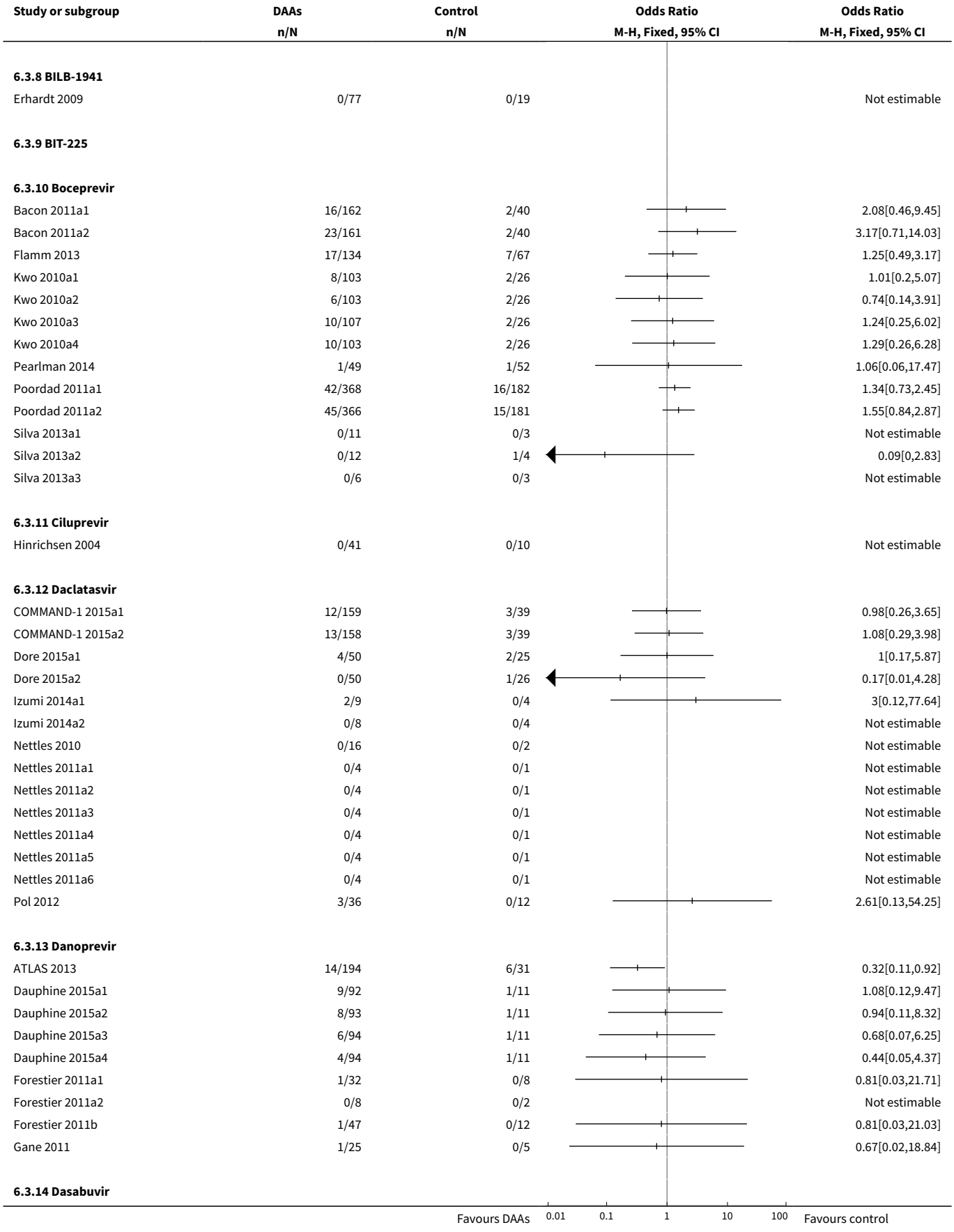
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
6.2.2 Trials with a low risk of bias				

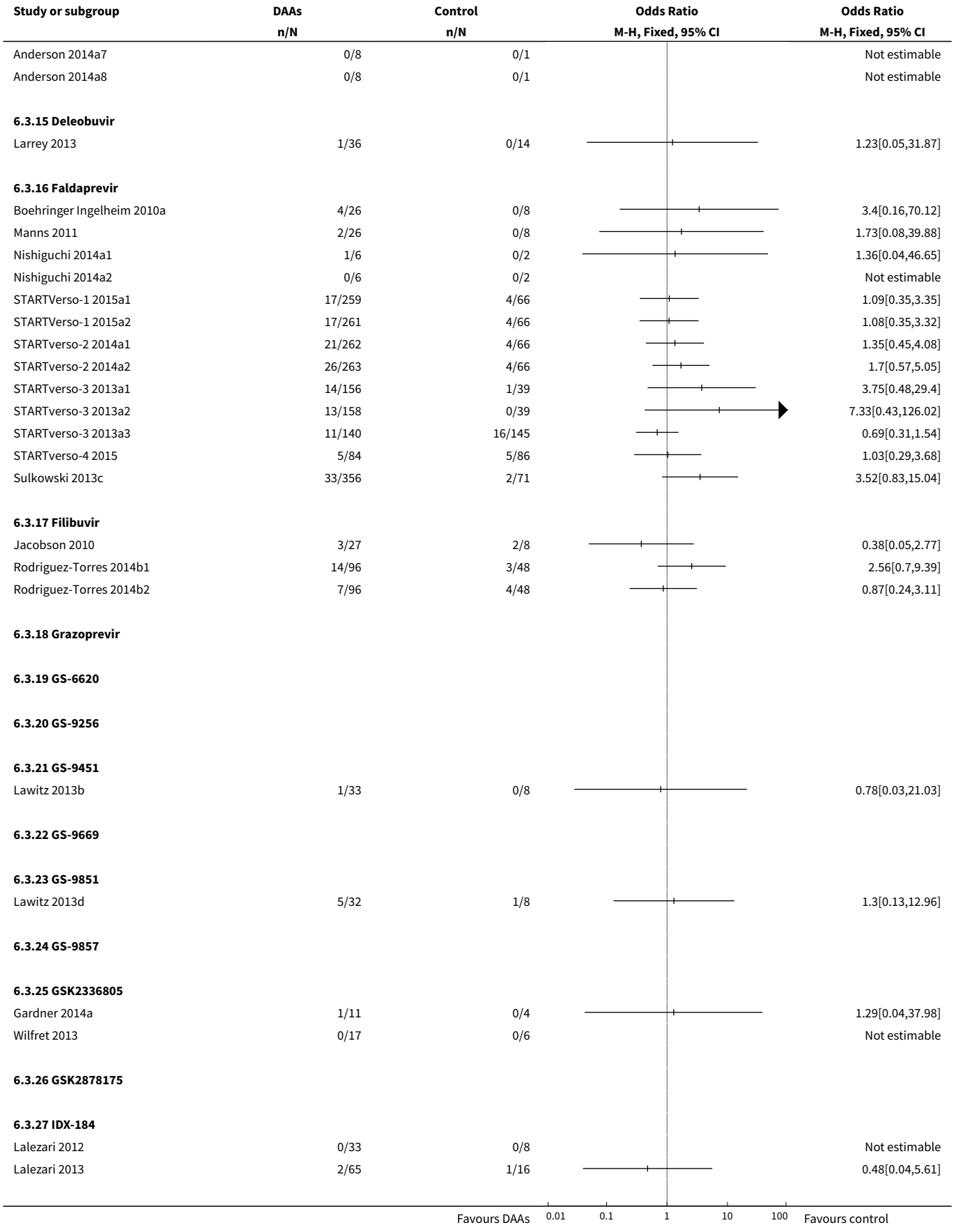


Analysis 6.3. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 3 Serious adverse events - according to type of DAA.

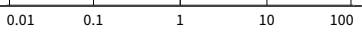
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.3.1 ABT-072				
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
6.3.2 ACH-2684				
6.3.3 Alisporivir				
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
6.3.4 ALS-2200				
6.3.5 Asunaprevir				
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
6.3.6 Balapiravir				
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
6.3.7 Beclabuvir				
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable



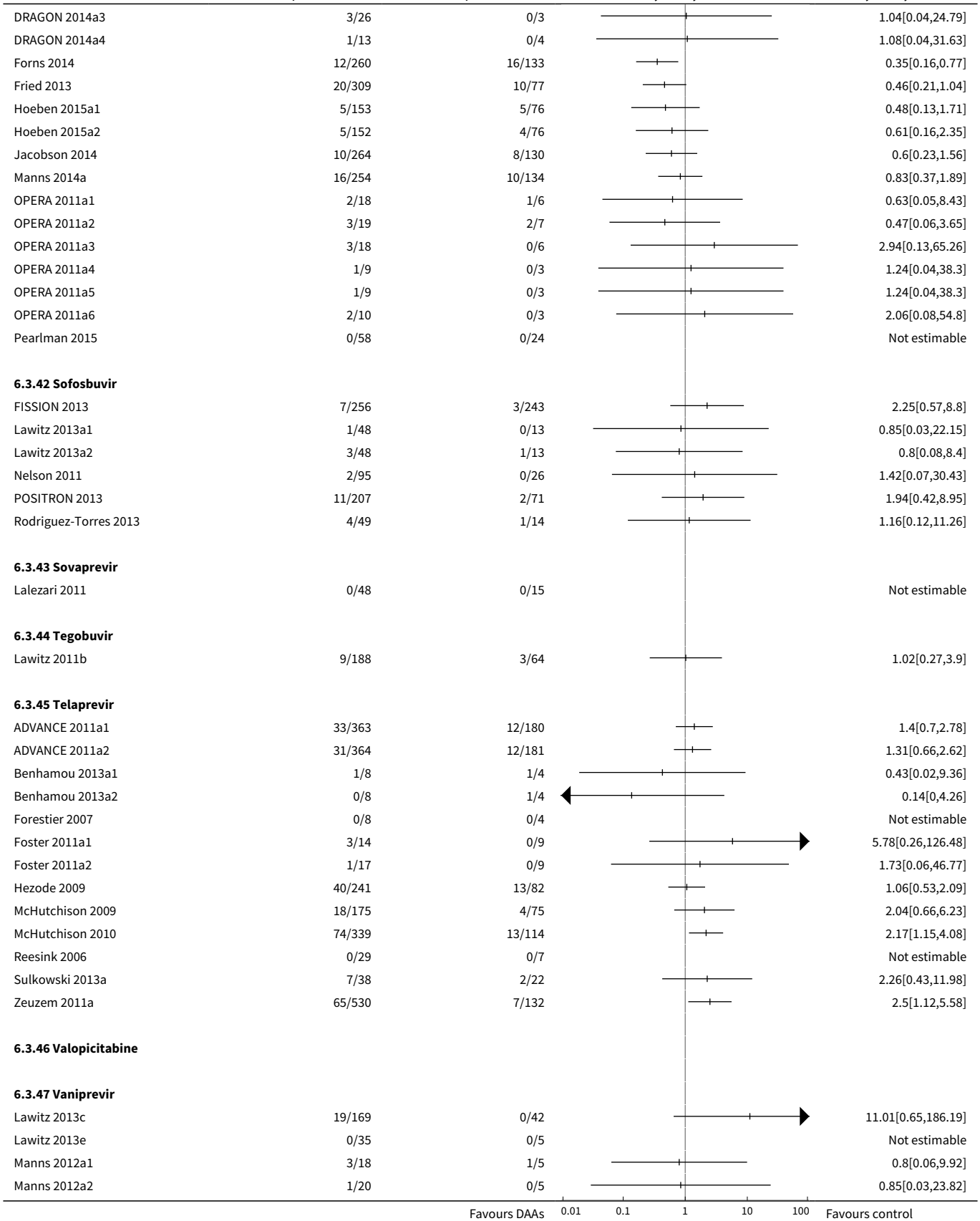




Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.3.28 INX-08189				
6.3.29 Ledispasvir				
Lawitz 2012a	0/59	0/12		Not estimable
6.3.30 Mericitabine				
Gane 2008	0/20	0/5		Not estimable
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
6.3.31 Narlaprevir				
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
6.3.32 Nesbuvir				
6.3.33 Odalasavir				
Gane 2015	0/18	0/12		Not estimable
6.3.34 Ombitasvir				
Sullivan 2012	0/28	0/9		Not estimable
6.3.35 Paritaprevir				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
6.3.36 PHX1766				
6.3.37 PPI-461				
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
6.3.38 PSI-352938				
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
6.3.39 Samatasvir				
Vince 2014	0/52	0/12		Not estimable
6.3.40 Setrobuvir				
Mallalieu 2014	0/27	0/8		Not estimable
6.3.41 Simeprevir				
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]

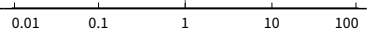


Favours DAAs | Favours control



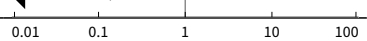
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pearlman 2015	0/58	0/24		Not estimable
6.3.42 Sofosbuvir				
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
6.3.43 Sovaprevir				
Lalezari 2011	0/48	0/15		Not estimable
6.3.44 Tegobuvir				
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
6.3.45 Telaprevir				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Forestier 2007	0/8	0/4		Not estimable
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Reesink 2006	0/29	0/7		Not estimable
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
6.3.46 Valopicitabine				
6.3.47 Vaniprevir				
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013e	0/35	0/5		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
6.3.48 VCH-759				
6.3.49 VCH-916				
6.3.50 Velpatasvir				
Lawitz 2015	0/39	0/17		Not estimable
6.3.51 VX-222				
6.3.52 Mixed				
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]



Analysis 6.4. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 4 Serious adverse events - according to group of DAA.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.4.1 Cyclophilin				
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
6.4.2 NS3/NS4A inhibitors				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]



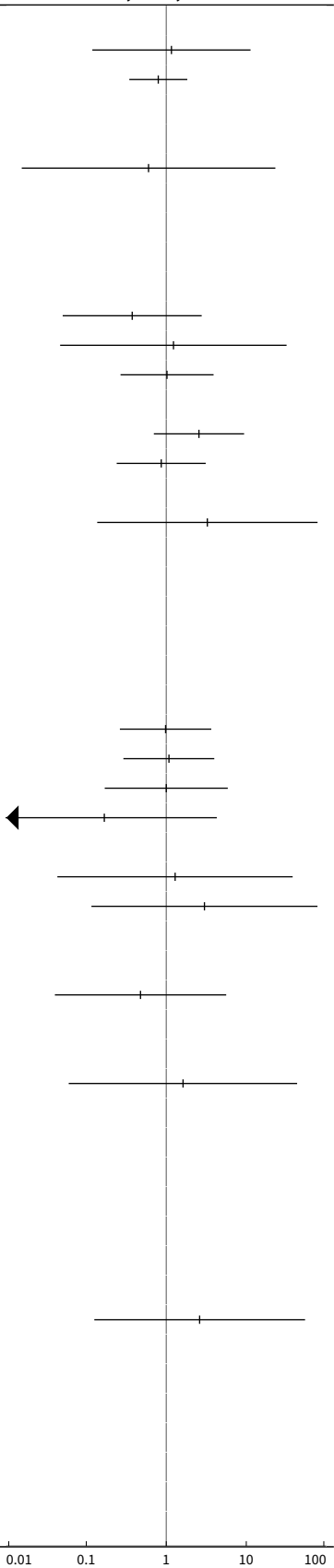
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forestier 2007	0/8	0/4		Not estimable
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hinrichsen 2004	0/41	0/10		Not estimable
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2011	0/48	0/15		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013e	0/35	0/5		Not estimable
Manns 2011	2/26	0/8		1.73[0.08,39.88]
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]

Favours DAAs 0.01 0.1 1 10 100 Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
6.4.3 NS5B inhibitors (NPI)				
Erhardt 2009	0/77	0/19		Not estimable
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Gane 2008	0/20	0/5		Not estimable
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable

Favours DAAs | Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
6.4.4 NS5B inhibitors (NNPI)				
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Mallalieu 2014	0/27	0/8		Not estimable
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Sims 2014	0/20	0/4		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
6.4.5 NS5A inhibitors				
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Lalezari 2012	0/33	0/8		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Sullivan 2012	0/28	0/9		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
6.4.6 VPU-ion channel inhibitors				
6.4.7 Mixed				



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]

Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 6.5. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 5 Serious adverse events - according to HIV-infection.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.5.1 With HIV-infection				
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
6.5.2 Without HIV-infection				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]

Favours DAAs 0.01 0.1 1 10 100 Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forestier 2007	0/8	0/4		Not estimable
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hinrichsen 2004	0/41	0/10		Not estimable
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2012	0/33	0/8		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]

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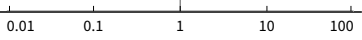
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Manns 2011	2/26	0/8		1.73[0.08,39.88]
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]



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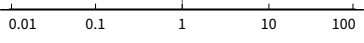
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
6.5.3 Mixed (with and without HIV-infection)				
6.5.4 Unclear				
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Gane 2008	0/20	0/5		Not estimable
Gane 2015	0/18	0/12		Not estimable
Lalezari 2011	0/48	0/15		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Sullivan 2012	0/28	0/9		Not estimable



Analysis 6.6. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 6 Serious adverse events - according to comorbidity.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.6.1 With comorbidity				
6.6.2 Without comorbidity				
6.6.3 Unclear				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forestier 2007	0/8	0/4		Not estimable
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Fried 2013	20/309	10/77		0.46[0.21,1.04]

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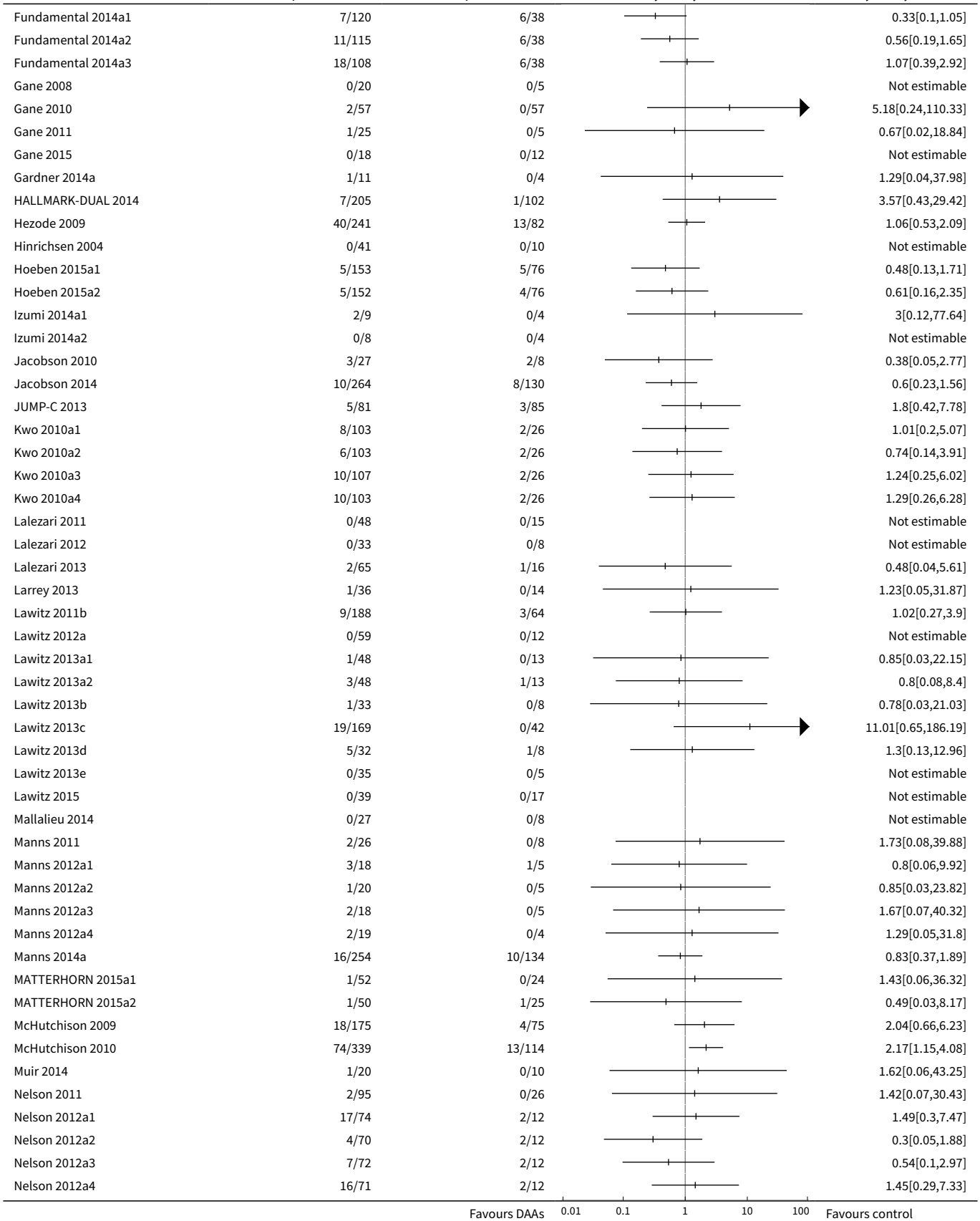


Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Reddy 2007	0/32	0/8		Not estimable
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]

Favours DAAs | Favours control

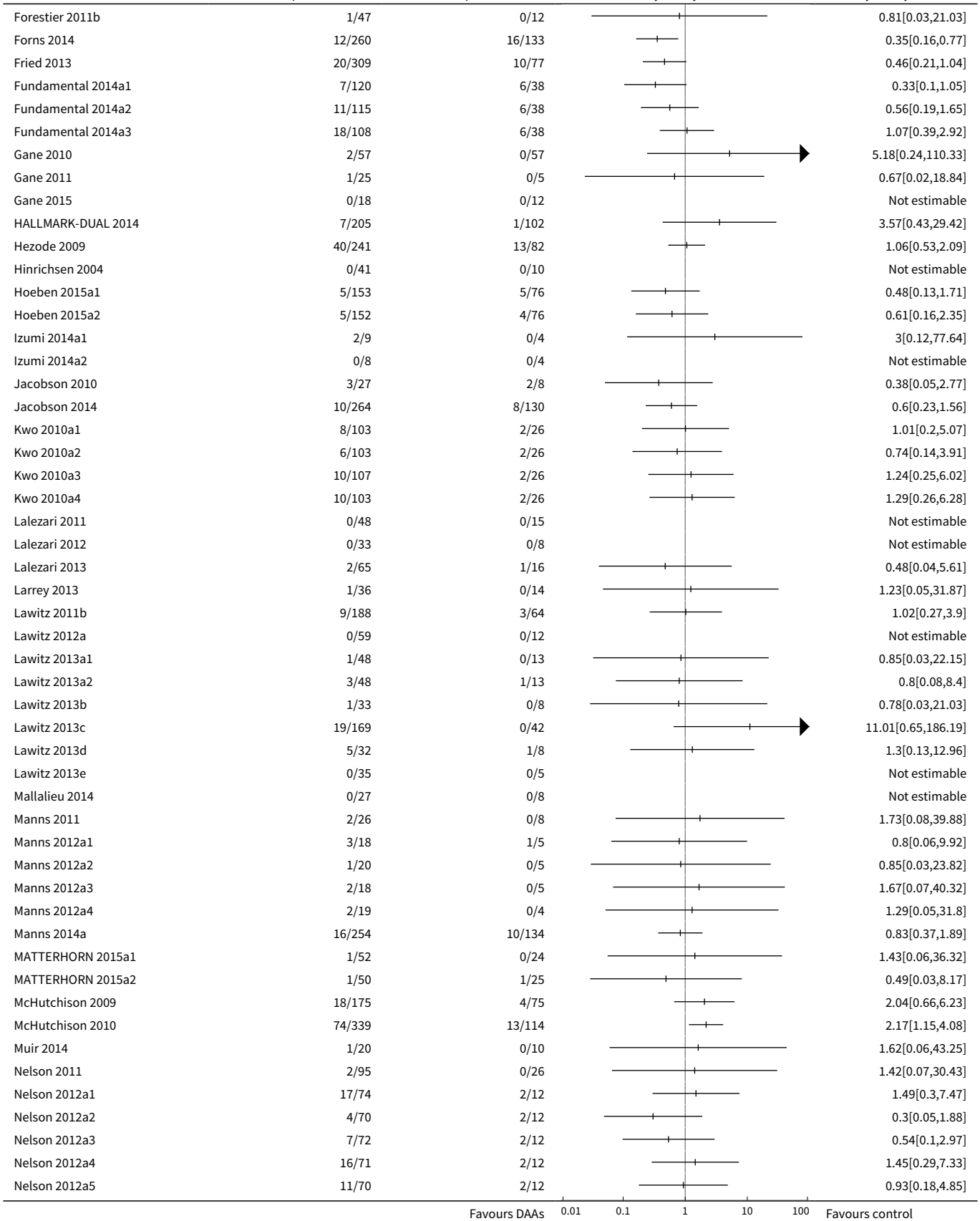
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]

Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 6.7. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 7 Serious adverse events - according to viral genotype.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.7.1 Genotype 1				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forestier 2007	0/8	0/4		Not estimable
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable

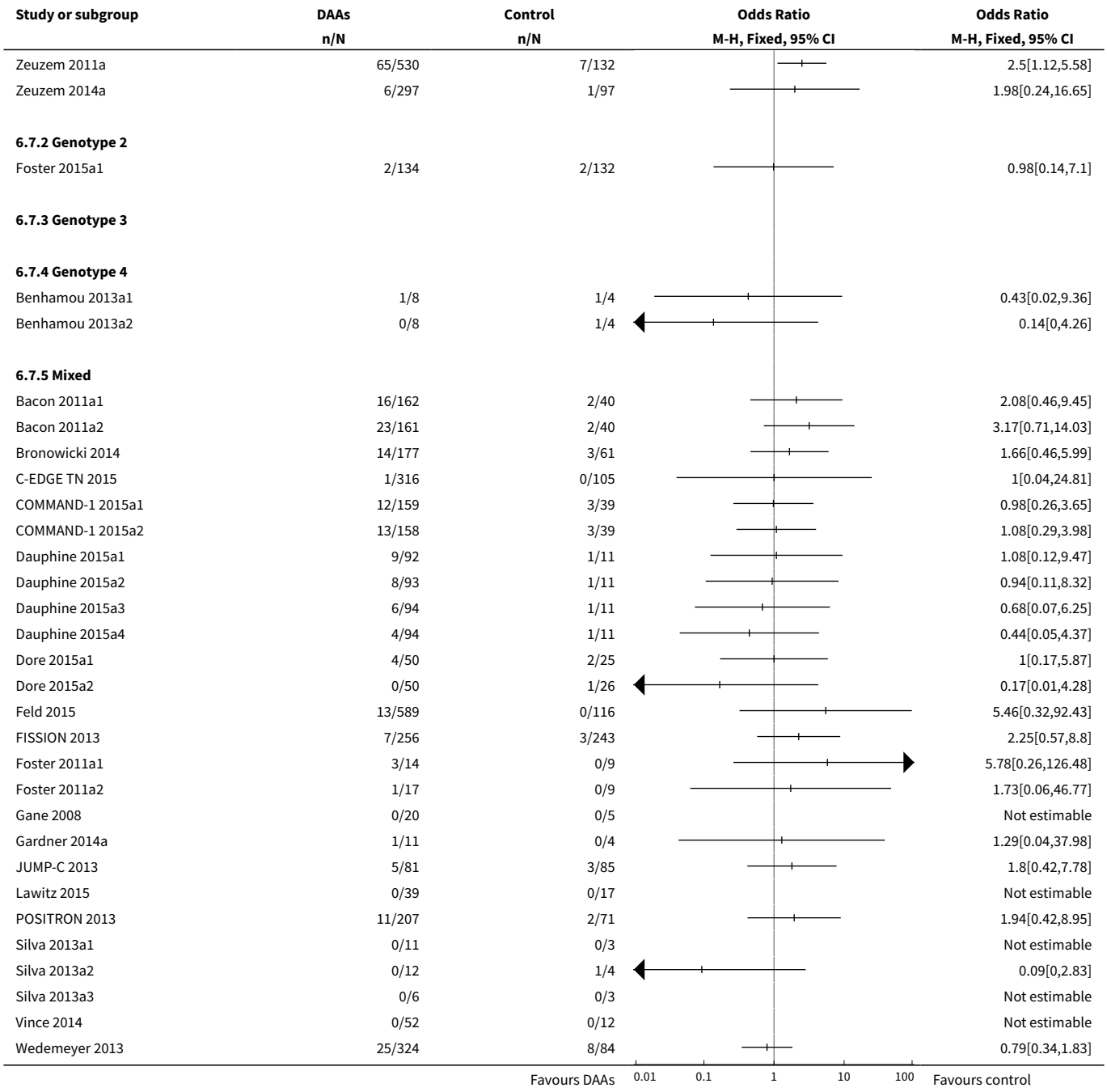
Favours DAAs 0.01 0.1 1 10 100 Favours control



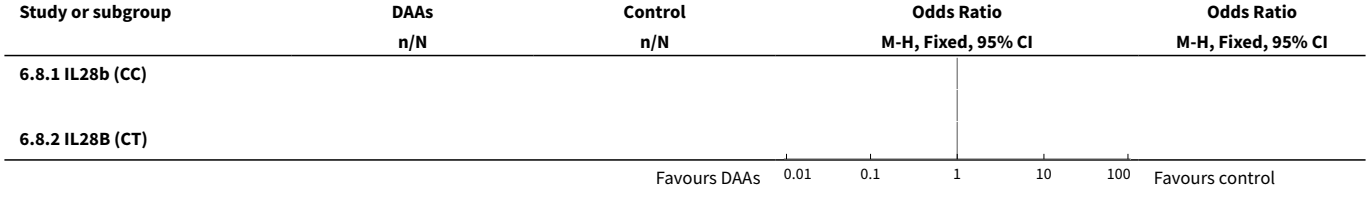
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hinrichsen 2004	0/41	0/10		Not estimable
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2011	0/48	0/15		Not estimable
Lalezari 2012	0/33	0/8		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Manns 2011	2/26	0/8		1.73[0.08,39.88]
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]

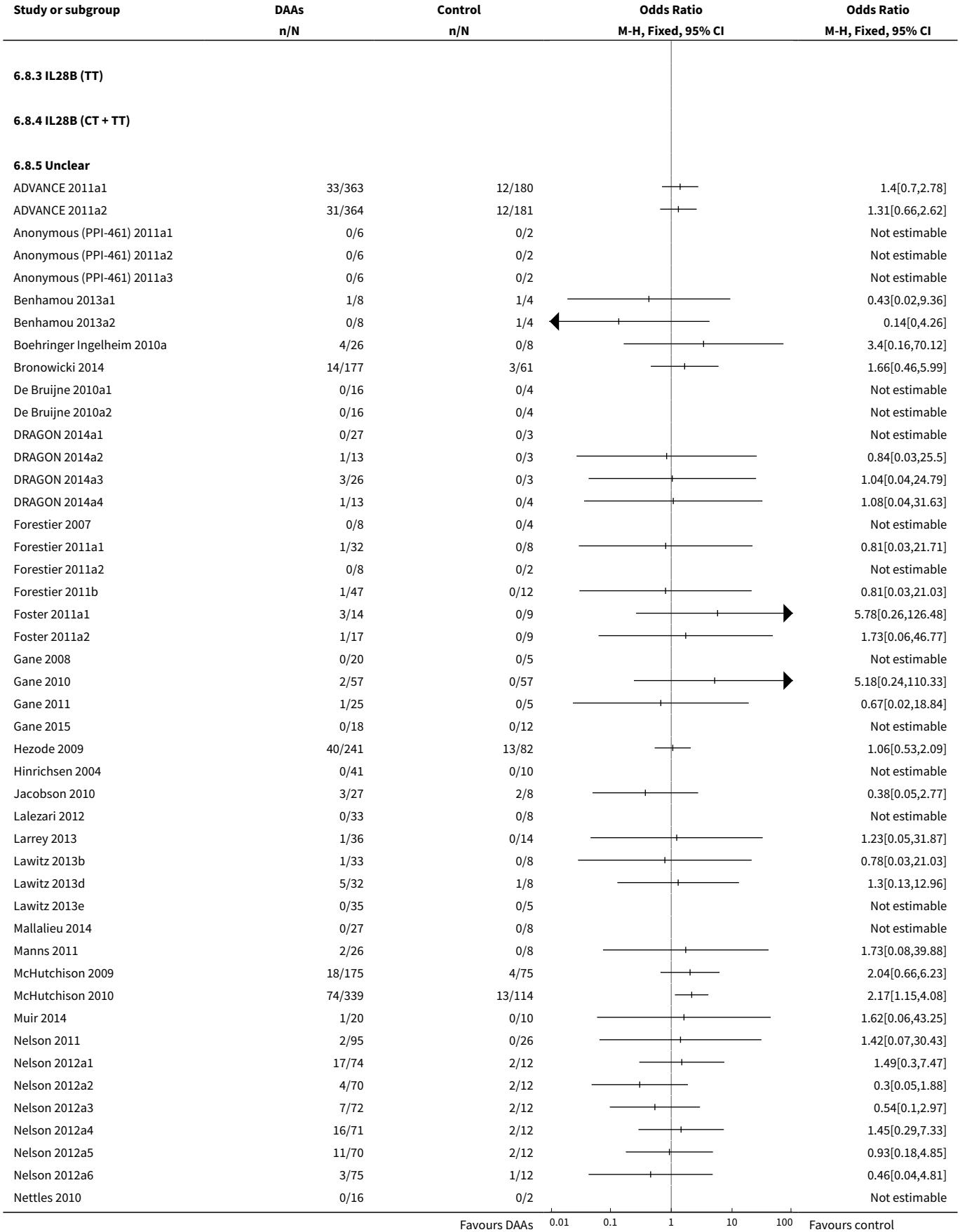
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
Reddy 2007	0/32	0/8		Not estimable
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Sims 2014	0/20	0/4		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Wilfret 2013	0/17	0/6		Not estimable

Favours DAAs Favours control



Analysis 6.8. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 8 Serious adverse events - according to human genotype (IL28b).





Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
Reddy 2007	0/32	0/8		Not estimable
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sullivan 2012	0/28	0/9		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
6.8.6 Mixed IL28b				
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]

Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2011	0/48	0/15		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2015	0/39	0/17		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]

Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pol 2012	3/36	0/12		2.61[0.13,54.25]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
		Favours DAAs	0.01 0.1 1 10 100	Favours control

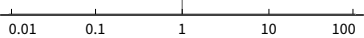
Analysis 6.9. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 9 Serious adverse events - according to Asian-region.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.9.1 From Asian region				
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
6.9.2 Not from Asian region				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
		Favours DAAs	0.01 0.1 1 10 100	Favours control

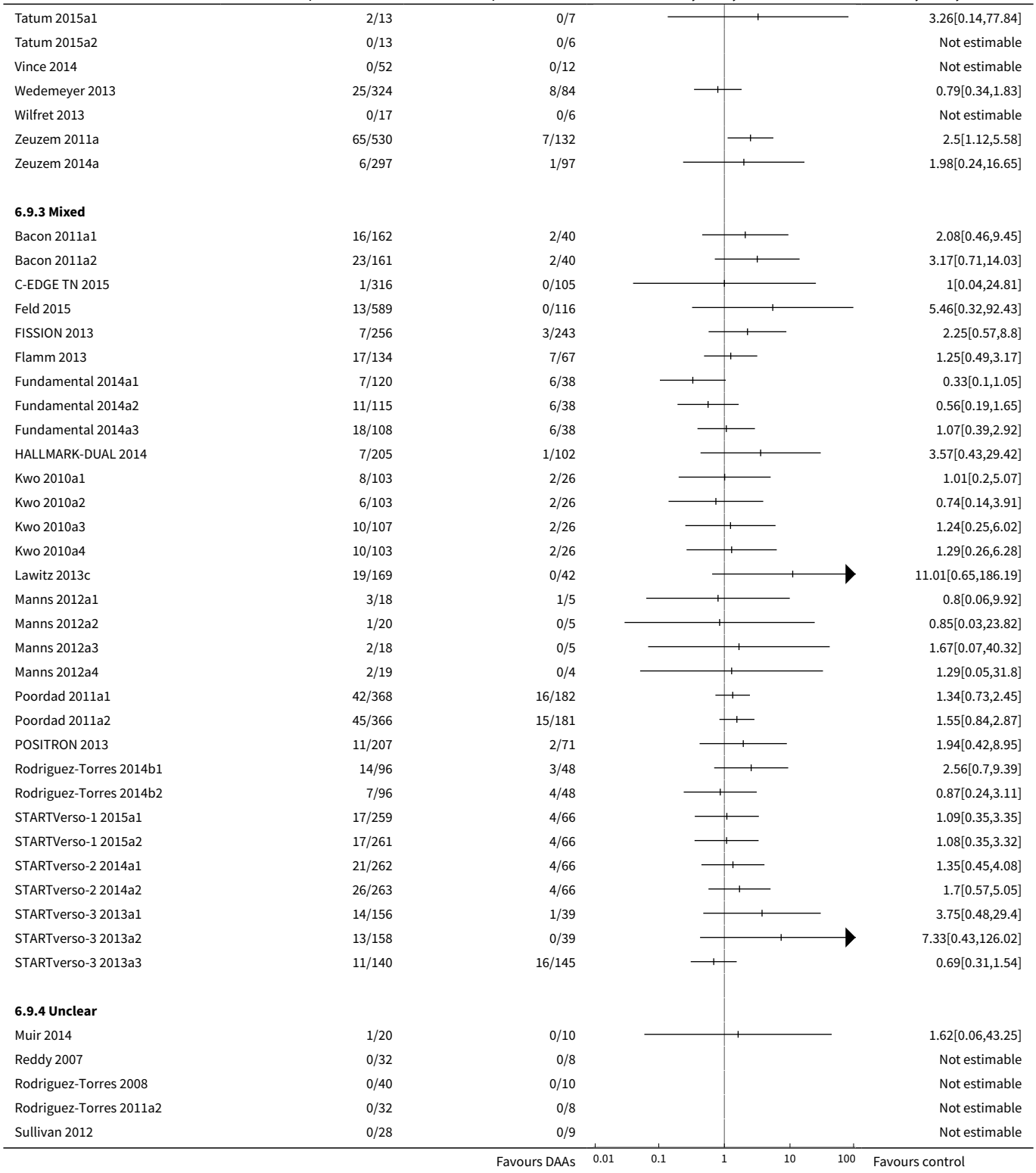
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Forestier 2007	0/8	0/4		Not estimable
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hinrichsen 2004	0/41	0/10		Not estimable
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Lalezari 2011	0/48	0/15		Not estimable
Lalezari 2012	0/33	0/8		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]

Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Manns 2011	2/26	0/8		1.73[0.08,39.88]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]

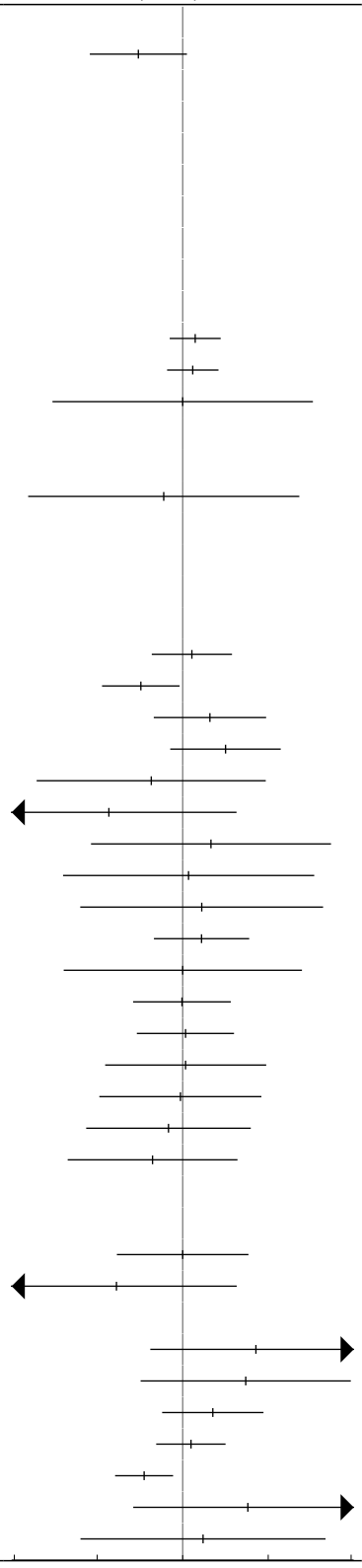


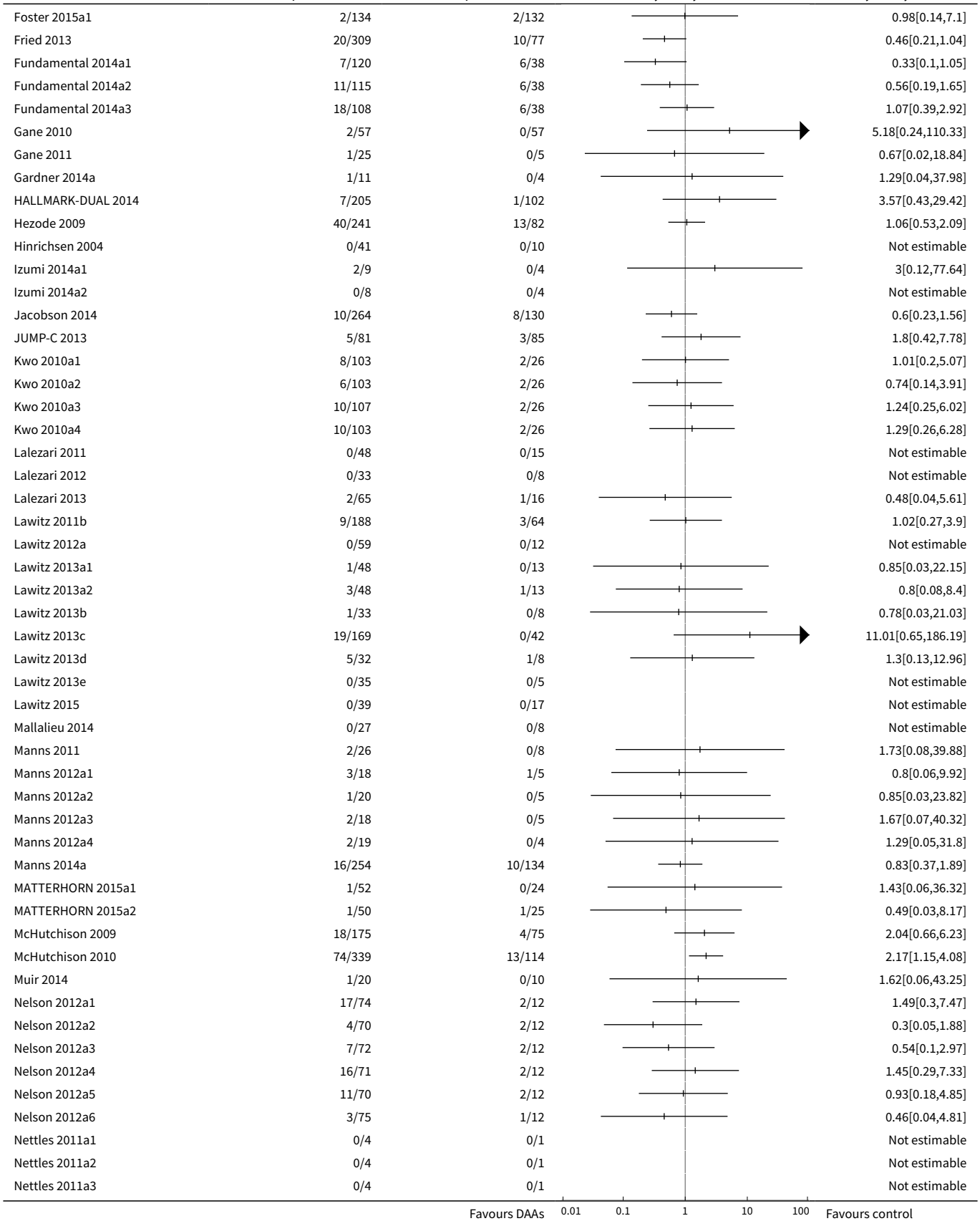
Favours DAAs Favours control



Analysis 6.10. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 10 Serious adverse events - according to specific ethnicities.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.10.1 White				
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Forestier 2007	0/8	0/4		Not estimable
Reesink 2006	0/29	0/7		Not estimable
6.10.2 Black				
6.10.3 Hispanic				
6.10.4 Mixed				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]



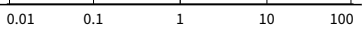


Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hinrichsen 2004	0/41	0/10		Not estimable
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2011	0/48	0/15		Not estimable
Lalezari 2012	0/33	0/8		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Manns 2011	2/26	0/8		1.73[0.08,39.88]
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Sullivan 2012	0/28	0/9		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
6.10.5 Unclear				
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]

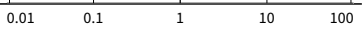
Favours DAAs Favours control

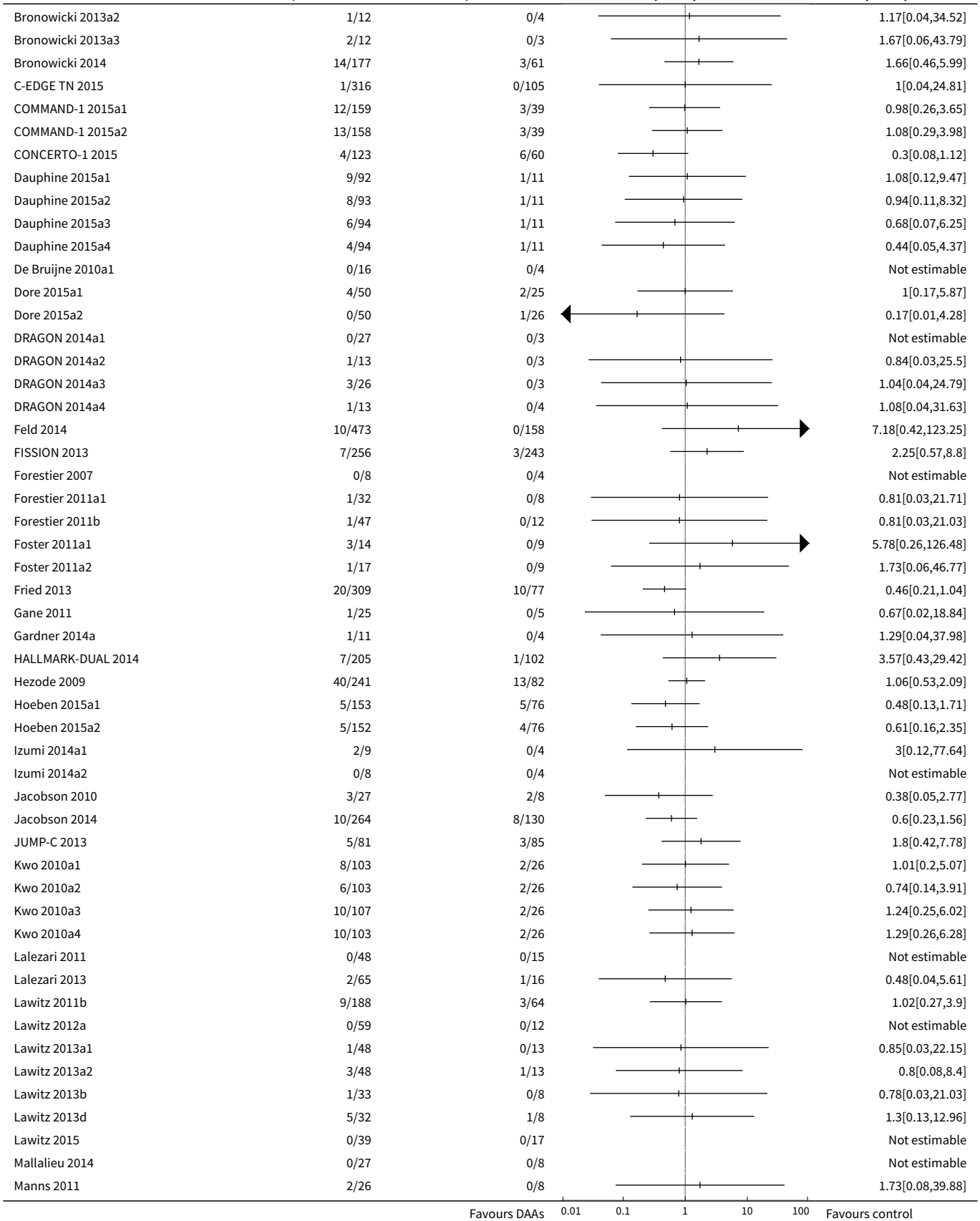
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Gane 2008	0/20	0/5		Not estimable
Gane 2015	0/18	0/12		Not estimable
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nettles 2010	0/16	0/2		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
Reddy 2007	0/32	0/8		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable



Analysis 6.12. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 12 Serious adverse events - according to prior treatment.

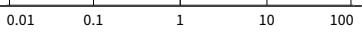
Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.12.1 Treatment-naive				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]



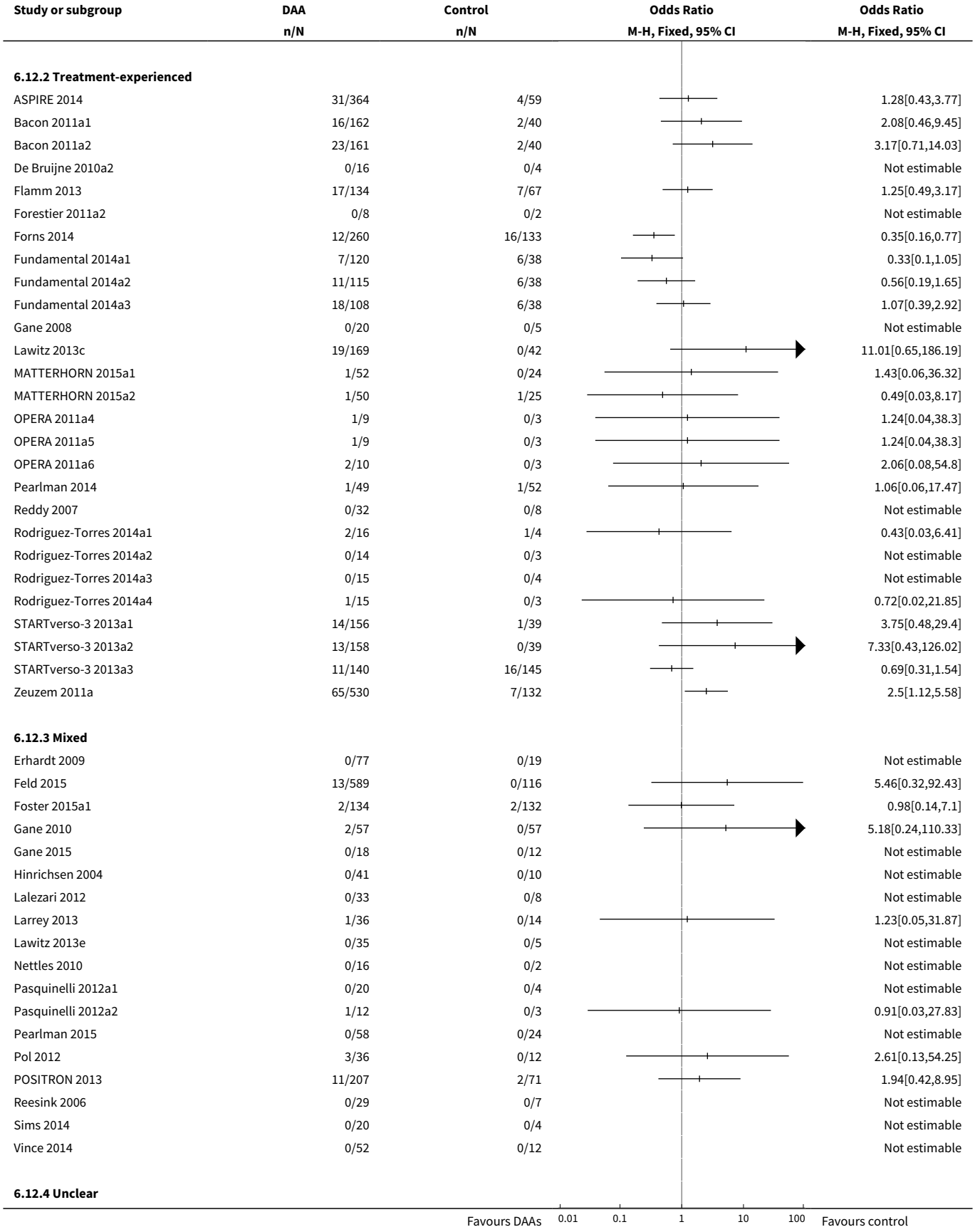


Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Forestier 2007	0/8	0/4		Not estimable
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2011	0/48	0/15		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2015	0/39	0/17		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Manns 2011	2/26	0/8		1.73[0.08,39.88]

Study or subgroup	DAA n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]

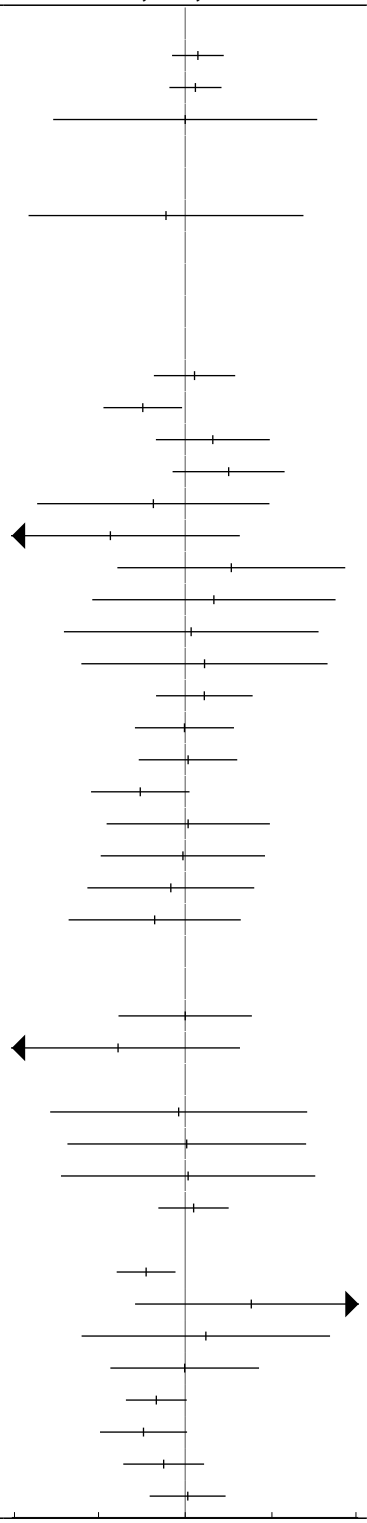


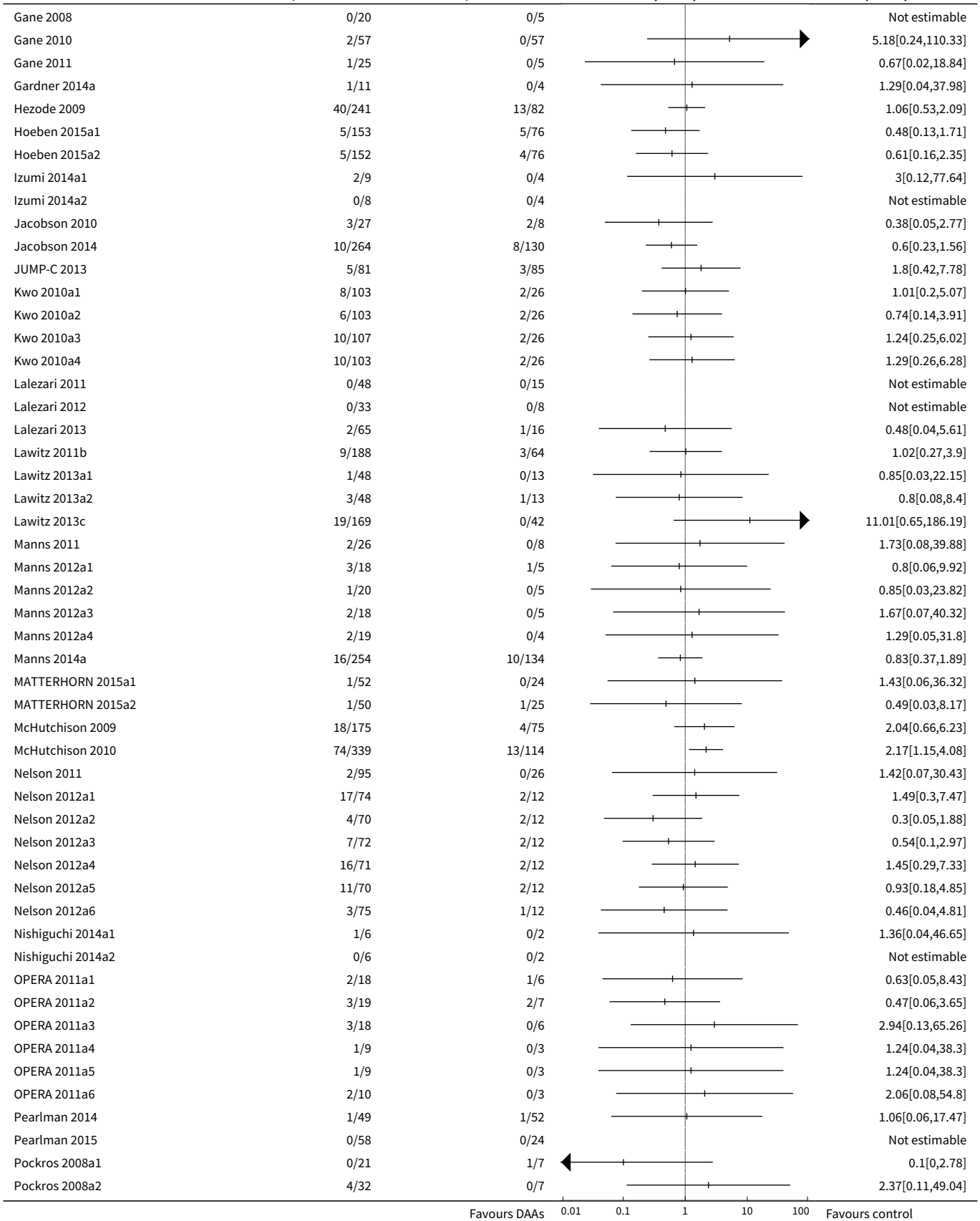
Favours DAAs Favours control



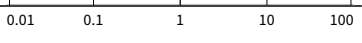
Analysis 6.13. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 13 Serious adverse events - according to interferon.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.13.1 Trials where both groups received interferon				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forestier 2007	0/8	0/4		Not estimable
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]





Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
6.13.2 Trials where neither group received interferon				
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Gane 2015	0/18	0/12		Not estimable
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hinrichsen 2004	0/41	0/10		Not estimable
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nettles 2010	0/16	0/2		Not estimable



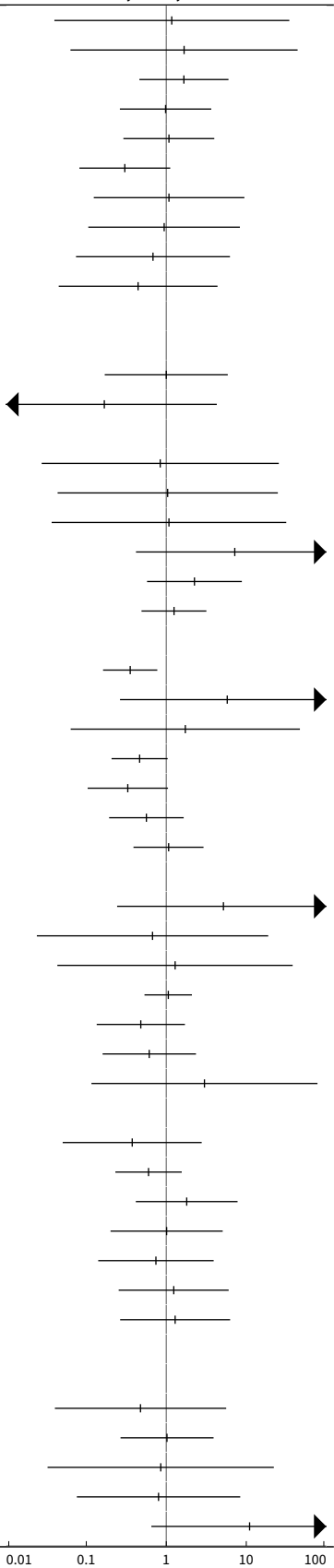
Favours DAAs Favours control

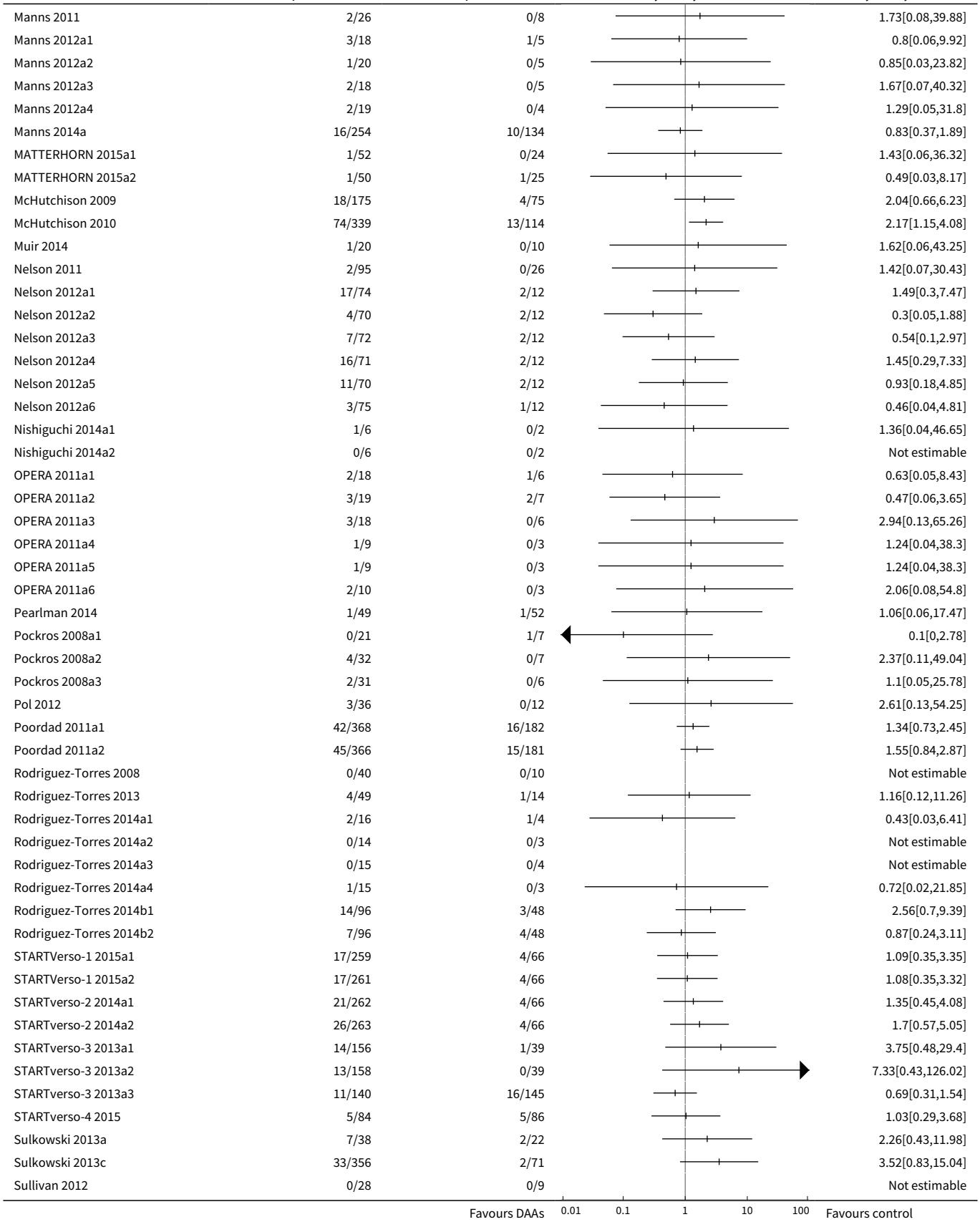
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Reddy 2007	0/32	0/8		Not estimable
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
6.13.3 Trials where only the experimental group received interferon				
6.13.4 Trials where only the control group received interferon				
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
		Favours DAAs	0.01 0.1 1 10 100	Favours control

Analysis 6.14. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 14 Serious adverse events - according to ribavirin.

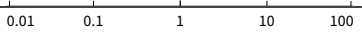
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.14.1 Trials where both groups received ribavirin				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
		Favours DAAs	0.01 0.1 1 10 100	Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Feld 2014	10/473	0/158		7.18[0.42,123.25]
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forestier 2007	0/8	0/4		Not estimable
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2011	0/48	0/15		Not estimable
Lalezari 2012	0/33	0/8		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]



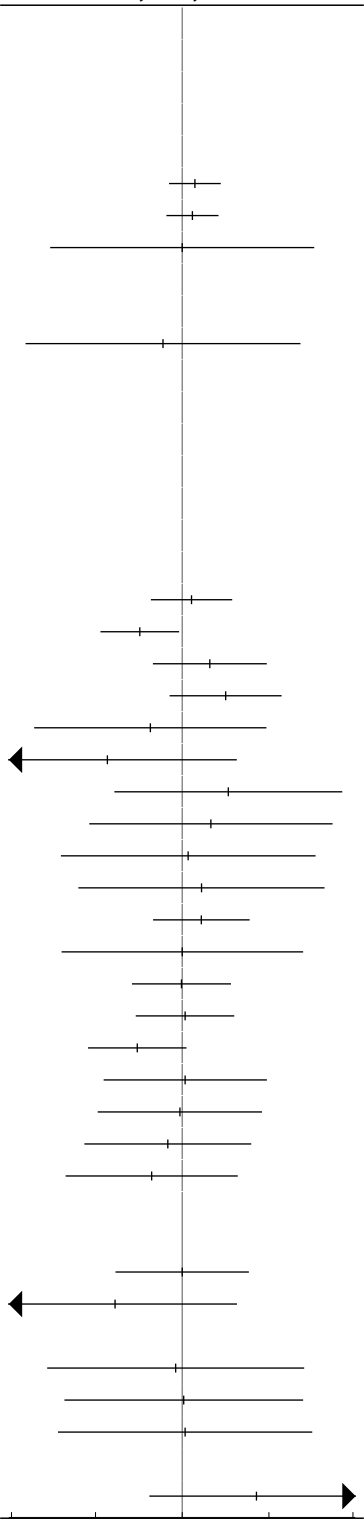


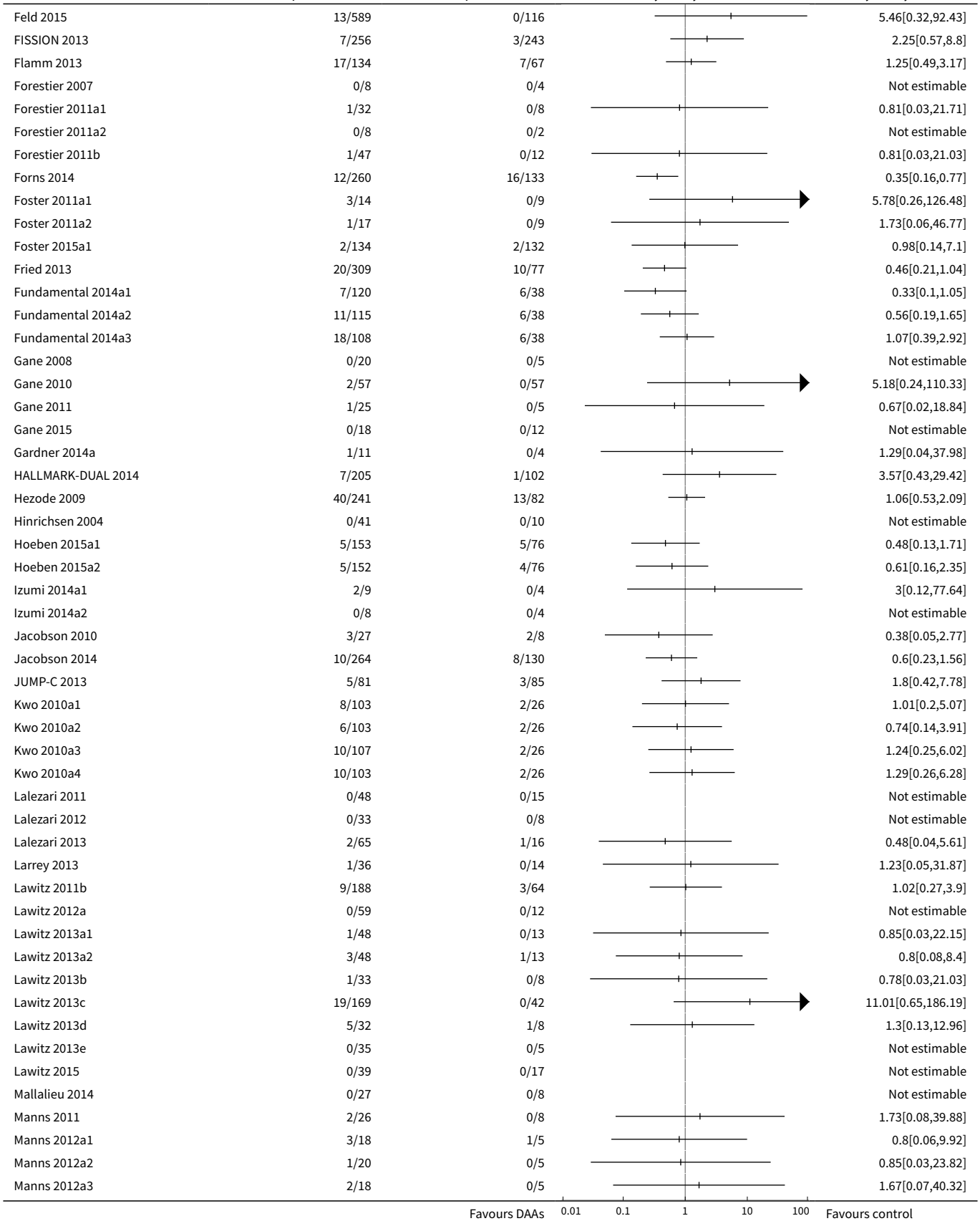
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]
6.14.2 Trials where neither group received ribavirin				
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2015	13/589	0/116		5.46[0.32,92.43]
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Gane 2015	0/18	0/12		Not estimable
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hinrichsen 2004	0/41	0/10		Not estimable
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Reddy 2007	0/32	0/8		Not estimable
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wilfret 2013	0/17	0/6		Not estimable
6.14.3 Trials where only the experimental group received ribavirin				
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
6.14.4 Trials where only the control group received ribavirin				
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Pearlman 2015	0/58	0/24		Not estimable



Analysis 6.15. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 15 Serious adverse events - according to chronic kidney disease.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.15.1 With chronic kidney disease				
6.15.2 Without chronic kidney disease				
6.15.3 Unclear				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]

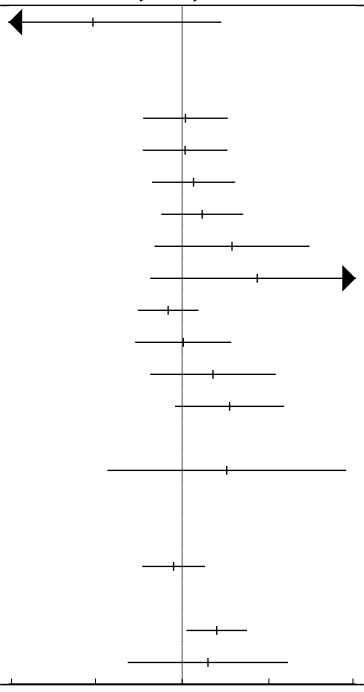




Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Reddy 2007	0/32	0/8		Not estimable
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Silva 2013a1	0/11	0/3		Not estimable

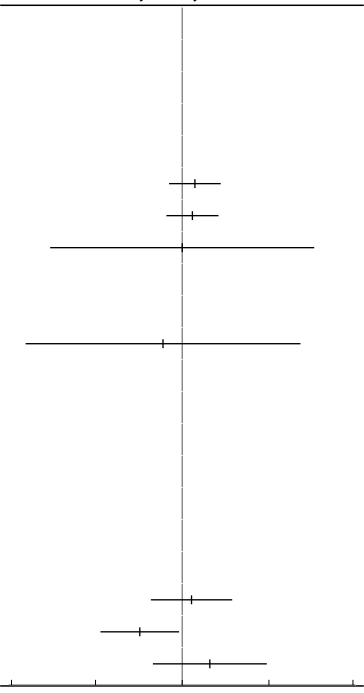
Favours DAAs Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]



Analysis 6.16. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 16 Serious adverse events - according to cryoglobulinaemia.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.16.1 With cryoglobulinaemia				
6.16.2 Without cryoglobulinaemia				
6.16.3 Unclear				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
FISSION 2013	7/256	3/243		2.25[0.57,8.8]
Flamm 2013	17/134	7/67		1.25[0.49,3.17]
Forestier 2007	0/8	0/4		Not estimable
Forestier 2011a1	1/32	0/8		0.81[0.03,21.71]
Forestier 2011a2	0/8	0/2		Not estimable
Forestier 2011b	1/47	0/12		0.81[0.03,21.03]
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Foster 2011a1	3/14	0/9		5.78[0.26,126.48]
Foster 2011a2	1/17	0/9		1.73[0.06,46.77]
Foster 2015a1	2/134	2/132		0.98[0.14,7.1]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Fundamental 2014a1	7/120	6/38		0.33[0.1,1.05]
Fundamental 2014a2	11/115	6/38		0.56[0.19,1.65]
Fundamental 2014a3	18/108	6/38		1.07[0.39,2.92]
Gane 2008	0/20	0/5		Not estimable
Gane 2010	2/57	0/57		5.18[0.24,110.33]
Gane 2011	1/25	0/5		0.67[0.02,18.84]
Gane 2015	0/18	0/12		Not estimable
Gardner 2014a	1/11	0/4		1.29[0.04,37.98]
HALLMARK-DUAL 2014	7/205	1/102		3.57[0.43,29.42]
Hezode 2009	40/241	13/82		1.06[0.53,2.09]
Hinrichsen 2004	0/41	0/10		Not estimable
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]

Favours DAA

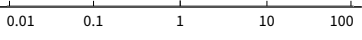
Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Izumi 2014a2	0/8	0/4		Not estimable
Jacobson 2010	3/27	2/8		0.38[0.05,2.77]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
JUMP-C 2013	5/81	3/85		1.8[0.42,7.78]
Kwo 2010a1	8/103	2/26		1.01[0.2,5.07]
Kwo 2010a2	6/103	2/26		0.74[0.14,3.91]
Kwo 2010a3	10/107	2/26		1.24[0.25,6.02]
Kwo 2010a4	10/103	2/26		1.29[0.26,6.28]
Lalezari 2011	0/48	0/15		Not estimable
Lalezari 2012	0/33	0/8		Not estimable
Lalezari 2013	2/65	1/16		0.48[0.04,5.61]
Larrey 2013	1/36	0/14		1.23[0.05,31.87]
Lawitz 2011b	9/188	3/64		1.02[0.27,3.9]
Lawitz 2012a	0/59	0/12		Not estimable
Lawitz 2013a1	1/48	0/13		0.85[0.03,22.15]
Lawitz 2013a2	3/48	1/13		0.8[0.08,8.4]
Lawitz 2013b	1/33	0/8		0.78[0.03,21.03]
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013d	5/32	1/8		1.3[0.13,12.96]
Lawitz 2013e	0/35	0/5		Not estimable
Lawitz 2015	0/39	0/17		Not estimable
Mallalieu 2014	0/27	0/8		Not estimable
Manns 2011	2/26	0/8		1.73[0.08,39.88]
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]

Favours DAA

Favours control

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Reddy 2007	0/32	0/8		Not estimable
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]

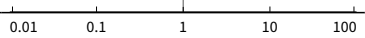


Favours DAA

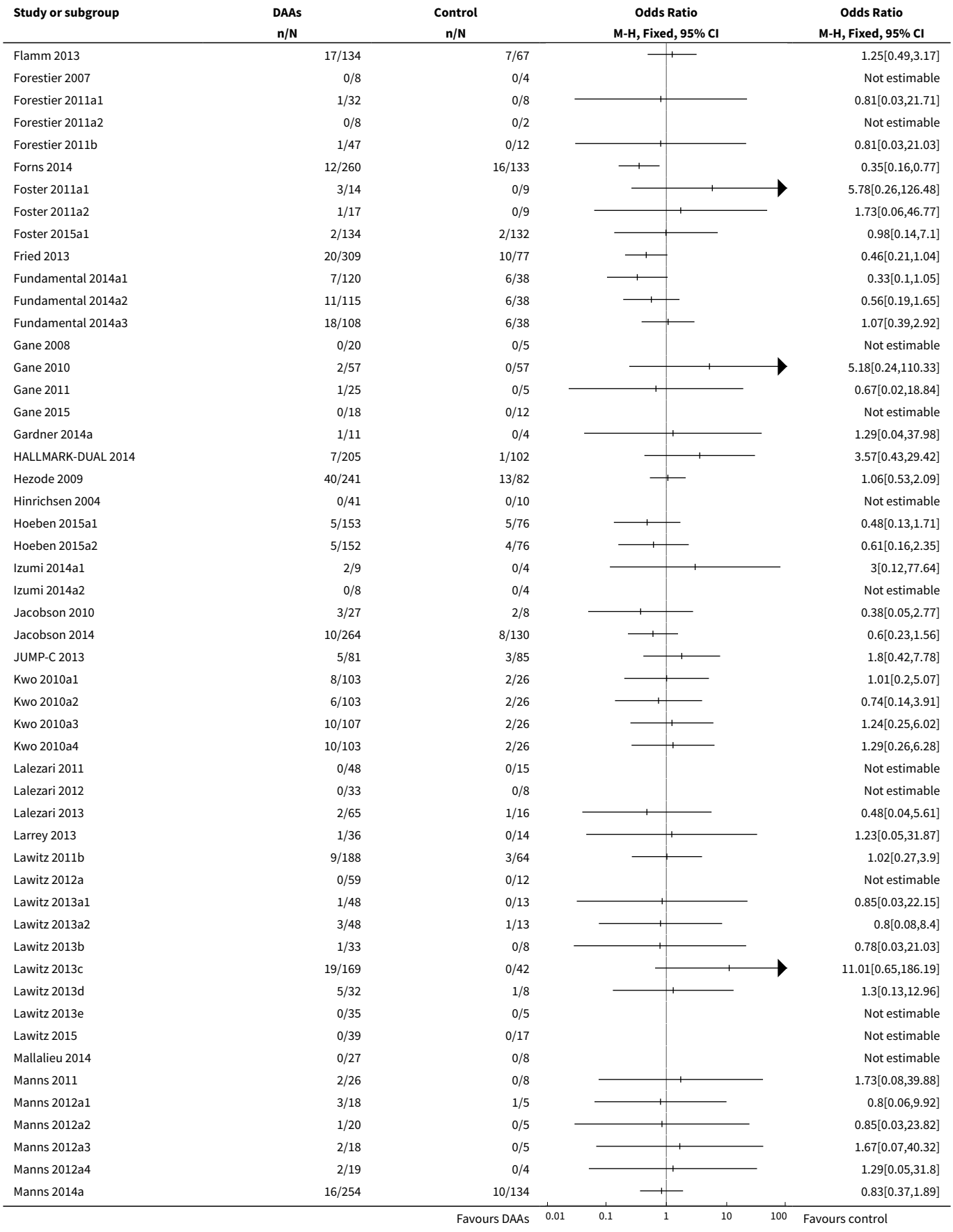
Favours control

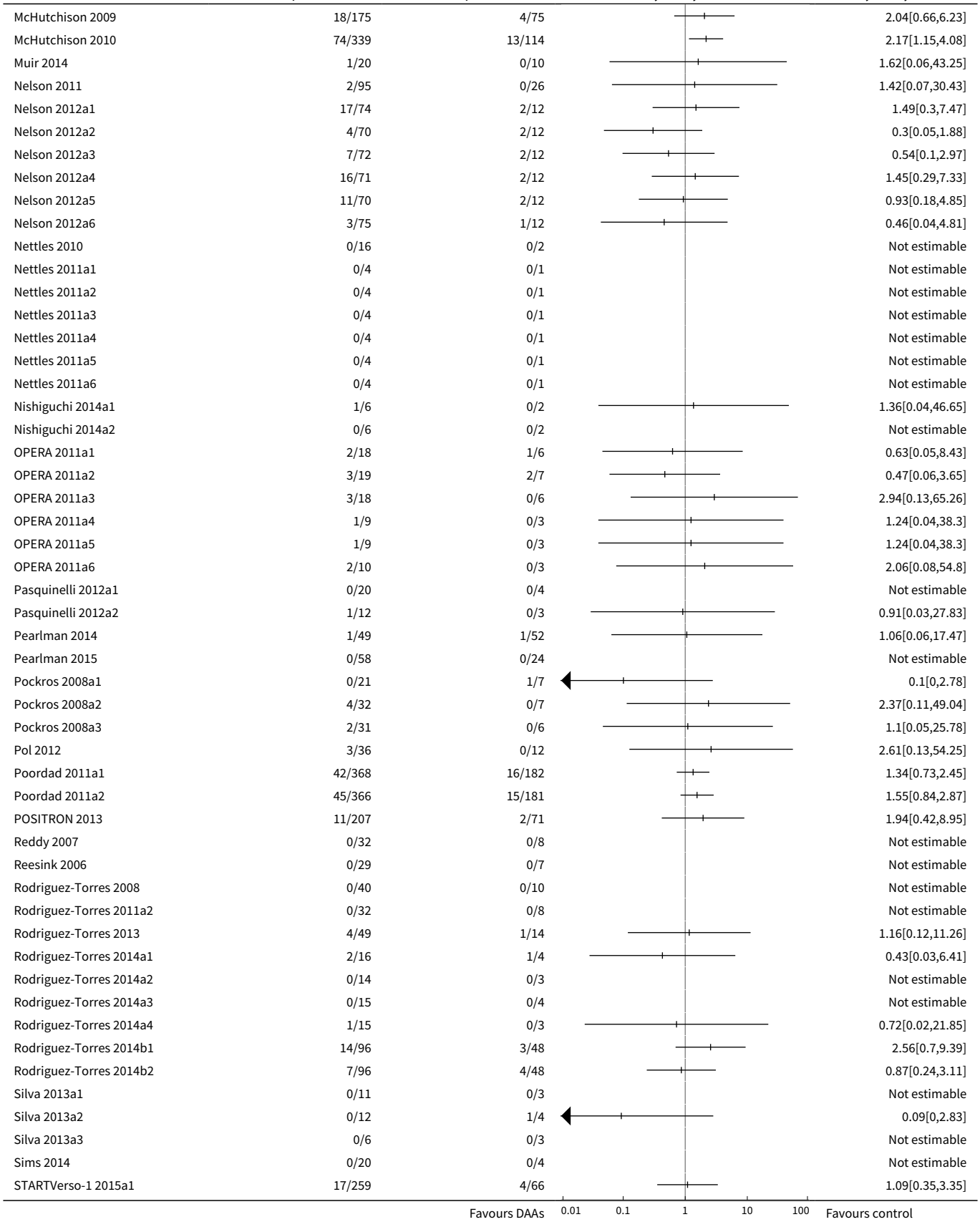
Analysis 6.17. Comparison 6 All DAA versus placebo/no intervention/other medical intervention (serious adverse events analyses), Outcome 17 Serious adverse events - according to DAA group as co-intervention.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
6.17.1 Trials where DAA were used as co-intervention				
MATTERHORN 2015a1	1/52	0/24		1.43[0.06,36.32]
MATTERHORN 2015a2	1/50	1/25		0.49[0.03,8.17]
6.17.2 Trials where DAA were not a co-intervention				
ADVANCE 2011a1	33/363	12/180		1.4[0.7,2.78]
ADVANCE 2011a2	31/364	12/181		1.31[0.66,2.62]
Anderson 2014a1	1/8	0/2		1[0.03,33.32]
Anderson 2014a2	0/8	0/2		Not estimable
Anderson 2014a3	0/8	0/2		Not estimable
Anderson 2014a4	1/8	0/1		0.6[0.02,23.07]
Anderson 2014a5	0/8	0/1		Not estimable
Anderson 2014a6	0/7	0/1		Not estimable
Anderson 2014a7	0/8	0/1		Not estimable
Anderson 2014a8	0/8	0/1		Not estimable
Anonymous (PPI-461) 2011a1	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a2	0/6	0/2		Not estimable
Anonymous (PPI-461) 2011a3	0/6	0/2		Not estimable
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
ATLAS 2013	14/194	6/31		0.32[0.11,0.92]
Bacon 2011a1	16/162	2/40		2.08[0.46,9.45]
Bacon 2011a2	23/161	2/40		3.17[0.71,14.03]
Benhamou 2013a1	1/8	1/4		0.43[0.02,9.36]
Benhamou 2013a2	0/8	1/4		0.14[0,4.26]
Boehringer Ingelheim 2010a	4/26	0/8		3.4[0.16,70.12]
Bronowicki 2013a1	2/12	0/4		2.14[0.08,54.22]
Bronowicki 2013a2	1/12	0/4		1.17[0.04,34.52]
Bronowicki 2013a3	2/12	0/3		1.67[0.06,43.79]
Bronowicki 2014	14/177	3/61		1.66[0.46,5.99]
C-EDGE TN 2015	1/316	0/105		1[0.04,24.81]
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
Dauphine 2015a1	9/92	1/11		1.08[0.12,9.47]
Dauphine 2015a2	8/93	1/11		0.94[0.11,8.32]
Dauphine 2015a3	6/94	1/11		0.68[0.07,6.25]
Dauphine 2015a4	4/94	1/11		0.44[0.05,4.37]
De Bruijne 2010a1	0/16	0/4		Not estimable
De Bruijne 2010a2	0/16	0/4		Not estimable
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Erhardt 2009	0/77	0/19		Not estimable
Feld 2014	10/473	0/158		7.18[0.42,123.25]
Feld 2015	13/589	0/116		5.46[0.32,92.43]
FISSION 2013	7/256	3/243		2.25[0.57,8.8]



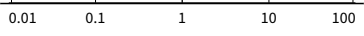
Favours DAAs — Favours control





Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
McHutchison 2009	18/175	4/75		2.04[0.66,6.23]
McHutchison 2010	74/339	13/114		2.17[1.15,4.08]
Muir 2014	1/20	0/10		1.62[0.06,43.25]
Nelson 2011	2/95	0/26		1.42[0.07,30.43]
Nelson 2012a1	17/74	2/12		1.49[0.3,7.47]
Nelson 2012a2	4/70	2/12		0.3[0.05,1.88]
Nelson 2012a3	7/72	2/12		0.54[0.1,2.97]
Nelson 2012a4	16/71	2/12		1.45[0.29,7.33]
Nelson 2012a5	11/70	2/12		0.93[0.18,4.85]
Nelson 2012a6	3/75	1/12		0.46[0.04,4.81]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Nishiguchi 2014a1	1/6	0/2		1.36[0.04,46.65]
Nishiguchi 2014a2	0/6	0/2		Not estimable
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]
Pasquinelli 2012a1	0/20	0/4		Not estimable
Pasquinelli 2012a2	1/12	0/3		0.91[0.03,27.83]
Pearlman 2014	1/49	1/52		1.06[0.06,17.47]
Pearlman 2015	0/58	0/24		Not estimable
Pockros 2008a1	0/21	1/7		0.1[0,2.78]
Pockros 2008a2	4/32	0/7		2.37[0.11,49.04]
Pockros 2008a3	2/31	0/6		1.1[0.05,25.78]
Pol 2012	3/36	0/12		2.61[0.13,54.25]
Poordad 2011a1	42/368	16/182		1.34[0.73,2.45]
Poordad 2011a2	45/366	15/181		1.55[0.84,2.87]
POSITRON 2013	11/207	2/71		1.94[0.42,8.95]
Reddy 2007	0/32	0/8		Not estimable
Reesink 2006	0/29	0/7		Not estimable
Rodriguez-Torres 2008	0/40	0/10		Not estimable
Rodriguez-Torres 2011a2	0/32	0/8		Not estimable
Rodriguez-Torres 2013	4/49	1/14		1.16[0.12,11.26]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
Rodriguez-Torres 2014b1	14/96	3/48		2.56[0.7,9.39]
Rodriguez-Torres 2014b2	7/96	4/48		0.87[0.24,3.11]
Silva 2013a1	0/11	0/3		Not estimable
Silva 2013a2	0/12	1/4		0.09[0,2.83]
Silva 2013a3	0/6	0/3		Not estimable
Sims 2014	0/20	0/4		Not estimable
STARTVerso-1 2015a1	17/259	4/66		1.09[0.35,3.35]

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
STARTVerso-1 2015a2	17/261	4/66		1.08[0.35,3.32]
STARTverso-2 2014a1	21/262	4/66		1.35[0.45,4.08]
STARTverso-2 2014a2	26/263	4/66		1.7[0.57,5.05]
STARTverso-3 2013a1	14/156	1/39		3.75[0.48,29.4]
STARTverso-3 2013a2	13/158	0/39		7.33[0.43,126.02]
STARTverso-3 2013a3	11/140	16/145		0.69[0.31,1.54]
STARTverso-4 2015	5/84	5/86		1.03[0.29,3.68]
Sulkowski 2013a	7/38	2/22		2.26[0.43,11.98]
Sulkowski 2013c	33/356	2/71		3.52[0.83,15.04]
Sullivan 2012	0/28	0/9		Not estimable
Tatum 2015a1	2/13	0/7		3.26[0.14,77.84]
Tatum 2015a2	0/13	0/6		Not estimable
Vince 2014	0/52	0/12		Not estimable
Wedemeyer 2013	25/324	8/84		0.79[0.34,1.83]
Wilfret 2013	0/17	0/6		Not estimable
Zeuzem 2011a	65/530	7/132		2.5[1.12,5.58]
Zeuzem 2014a	6/297	1/97		1.98[0.24,16.65]

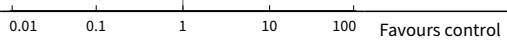


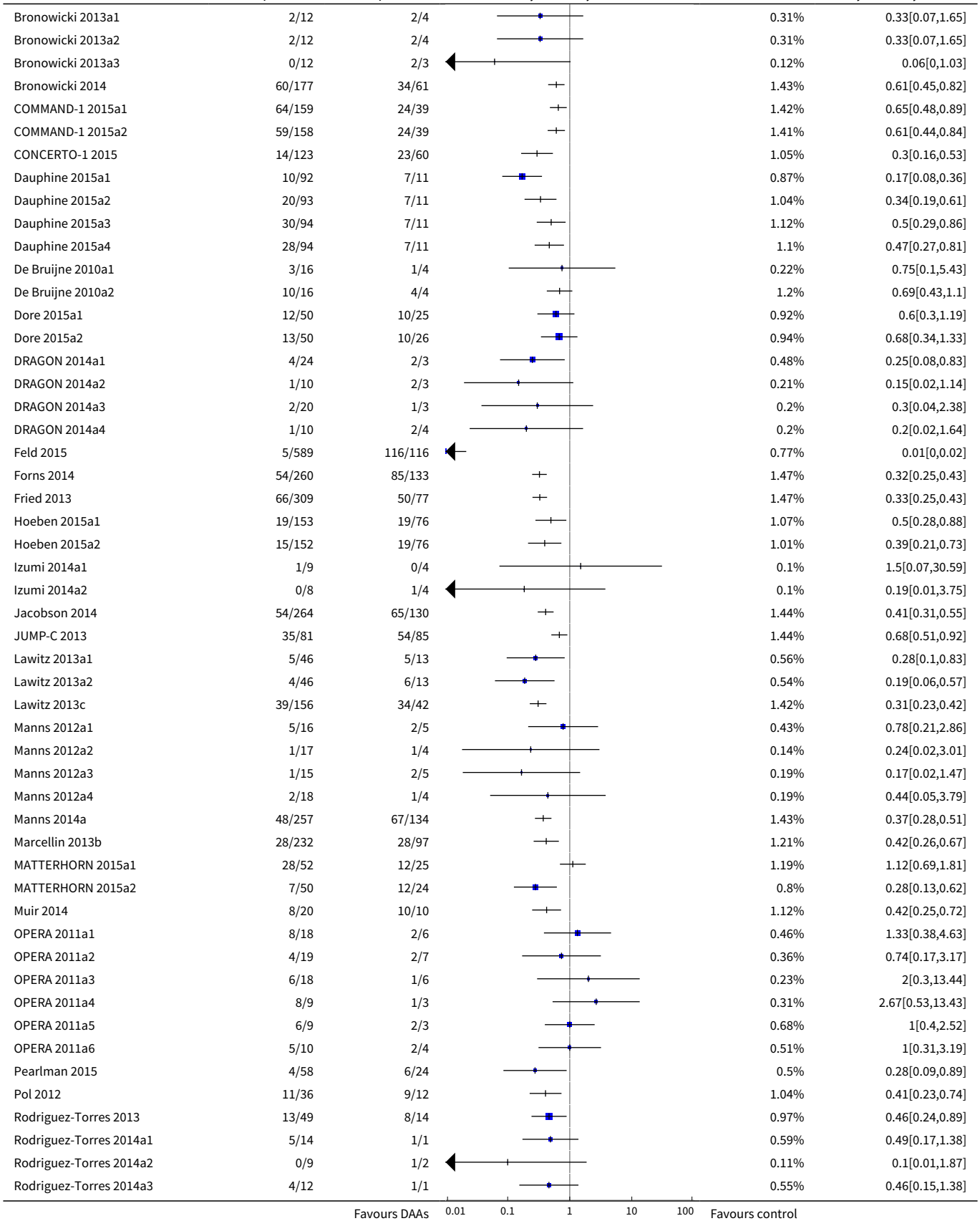
Comparison 7. All DAA versus placebo/no intervention/other medical intervention (sustained virological response analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Without sustained virological response	107	17101	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.48, 0.59]
1.1 Trials assessing DAAs on or on the way to the market	60	6886	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.52]
1.2 Trials assessing DAAs withdrawn from market	43	9075	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.55, 0.69]
1.3 Trials using other medical intervention as control group	3	862	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.36, 1.82]
1.4 Trials using other medical intervention as experimental group	1	278	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.17, 0.29]

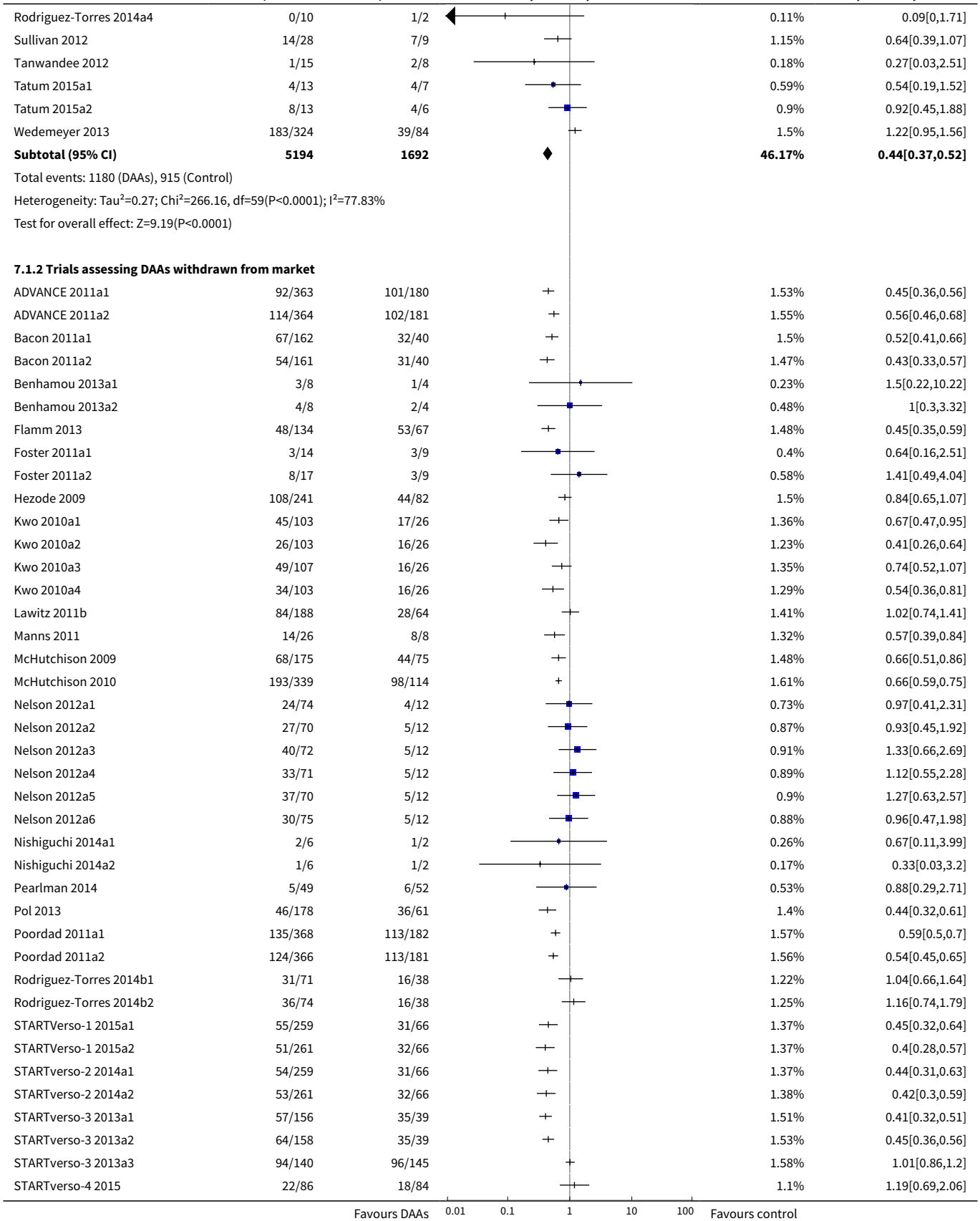
Analysis 7.1. Comparison 7 All DAA versus placebo/no intervention/other medical intervention (sustained virological response analyses), Outcome 1 Without sustained virological response.

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Trials assessing DAAs on or on the way to the market					
ASPIRE 2014	90/364	44/59		1.51%	0.33[0.26,0.42]
ATLAS 2013	46/194	18/31		1.31%	0.41[0.28,0.6]

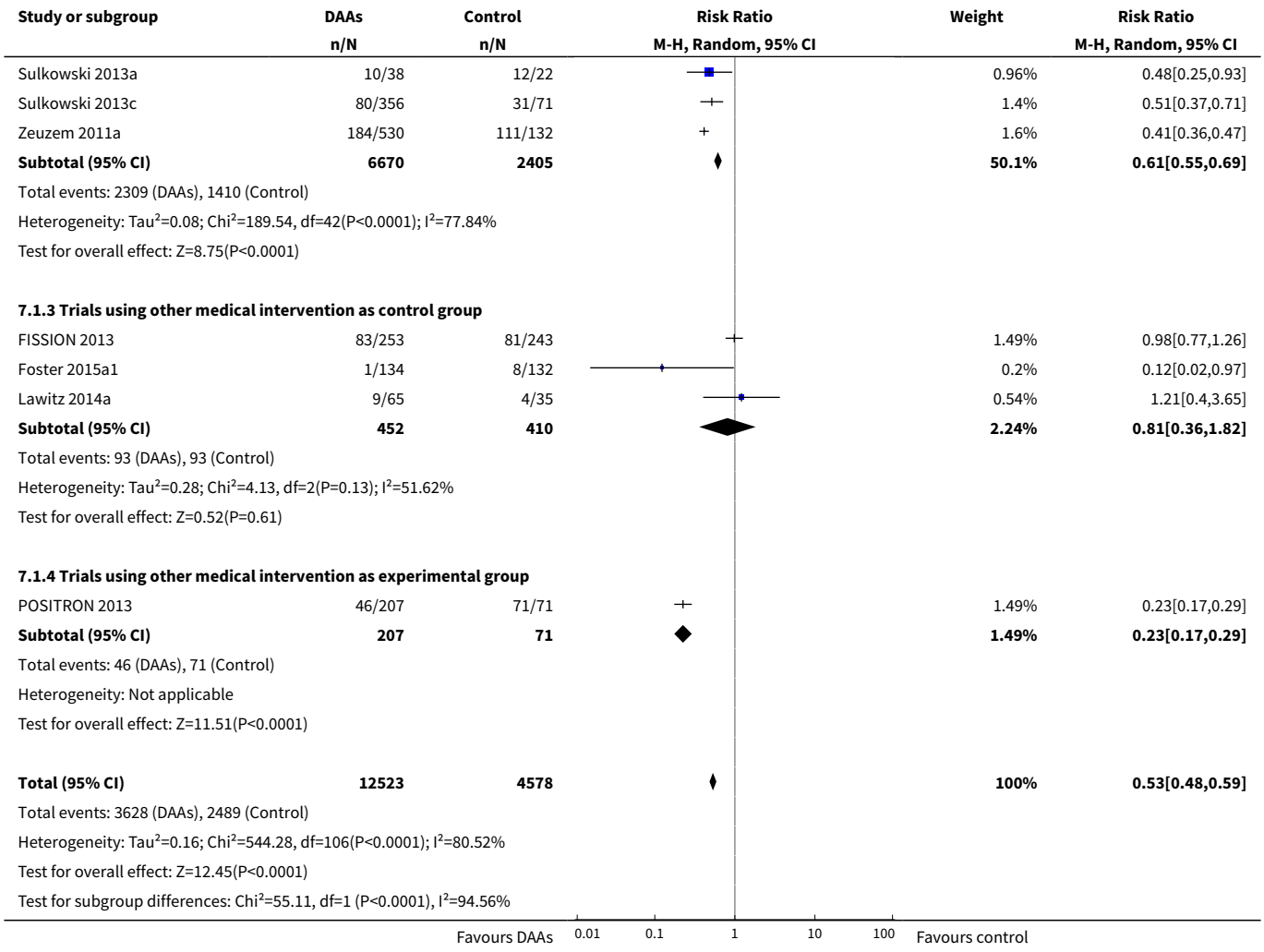




Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bronowicki 2013a1	2/12	2/4		0.31%	0.33[0.07,1.65]
Bronowicki 2013a2	2/12	2/4		0.31%	0.33[0.07,1.65]
Bronowicki 2013a3	0/12	2/3		0.12%	0.06[0,1.03]
Bronowicki 2014	60/177	34/61		1.43%	0.61[0.45,0.82]
COMMAND-1 2015a1	64/159	24/39		1.42%	0.65[0.48,0.89]
COMMAND-1 2015a2	59/158	24/39		1.41%	0.61[0.44,0.84]
CONCERTO-1 2015	14/123	23/60		1.05%	0.3[0.16,0.53]
Dauphine 2015a1	10/92	7/11		0.87%	0.17[0.08,0.36]
Dauphine 2015a2	20/93	7/11		1.04%	0.34[0.19,0.61]
Dauphine 2015a3	30/94	7/11		1.12%	0.5[0.29,0.86]
Dauphine 2015a4	28/94	7/11		1.1%	0.47[0.27,0.81]
De Bruijne 2010a1	3/16	1/4		0.22%	0.75[0.1,5.43]
De Bruijne 2010a2	10/16	4/4		1.2%	0.69[0.43,1.1]
Dore 2015a1	12/50	10/25		0.92%	0.6[0.3,1.19]
Dore 2015a2	13/50	10/26		0.94%	0.68[0.34,1.33]
DRAGON 2014a1	4/24	2/3		0.48%	0.25[0.08,0.83]
DRAGON 2014a2	1/10	2/3		0.21%	0.15[0.02,1.14]
DRAGON 2014a3	2/20	1/3		0.2%	0.3[0.04,2.38]
DRAGON 2014a4	1/10	2/4		0.2%	0.2[0.02,1.64]
Feld 2015	5/589	116/116		0.77%	0.01[0,0.02]
Forns 2014	54/260	85/133		1.47%	0.32[0.25,0.43]
Fried 2013	66/309	50/77		1.47%	0.33[0.25,0.43]
Hoeben 2015a1	19/153	19/76		1.07%	0.5[0.28,0.88]
Hoeben 2015a2	15/152	19/76		1.01%	0.39[0.21,0.73]
Izumi 2014a1	1/9	0/4		0.1%	1.5[0.07,30.59]
Izumi 2014a2	0/8	1/4		0.1%	0.19[0.01,3.75]
Jacobson 2014	54/264	65/130		1.44%	0.41[0.31,0.55]
JUMP-C 2013	35/81	54/85		1.44%	0.68[0.51,0.92]
Lawitz 2013a1	5/46	5/13		0.56%	0.28[0.1,0.83]
Lawitz 2013a2	4/46	6/13		0.54%	0.19[0.06,0.57]
Lawitz 2013c	39/156	34/42		1.42%	0.31[0.23,0.42]
Manns 2012a1	5/16	2/5		0.43%	0.78[0.21,2.86]
Manns 2012a2	1/17	1/4		0.14%	0.24[0.02,3.01]
Manns 2012a3	1/15	2/5		0.19%	0.17[0.02,1.47]
Manns 2012a4	2/18	1/4		0.19%	0.44[0.05,3.79]
Manns 2014a	48/257	67/134		1.43%	0.37[0.28,0.51]
Marcellin 2013b	28/232	28/97		1.21%	0.42[0.26,0.67]
MATTERHORN 2015a1	28/52	12/25		1.19%	1.12[0.69,1.81]
MATTERHORN 2015a2	7/50	12/24		0.8%	0.28[0.13,0.62]
Muir 2014	8/20	10/10		1.12%	0.42[0.25,0.72]
OPERA 2011a1	8/18	2/6		0.46%	1.33[0.38,4.63]
OPERA 2011a2	4/19	2/7		0.36%	0.74[0.17,3.17]
OPERA 2011a3	6/18	1/6		0.23%	2[0.3,13.44]
OPERA 2011a4	8/9	1/3		0.31%	2.67[0.53,13.43]
OPERA 2011a5	6/9	2/3		0.68%	1[0.4,2.52]
OPERA 2011a6	5/10	2/4		0.51%	1[0.31,3.19]
Pearlman 2015	4/58	6/24		0.5%	0.28[0.09,0.89]
Pol 2012	11/36	9/12		1.04%	0.41[0.23,0.74]
Rodriguez-Torres 2013	13/49	8/14		0.97%	0.46[0.24,0.89]
Rodriguez-Torres 2014a1	5/14	1/1		0.59%	0.49[0.17,1.38]
Rodriguez-Torres 2014a2	0/9	1/2		0.11%	0.1[0.01,1.87]
Rodriguez-Torres 2014a3	4/12	1/1		0.55%	0.46[0.15,1.38]



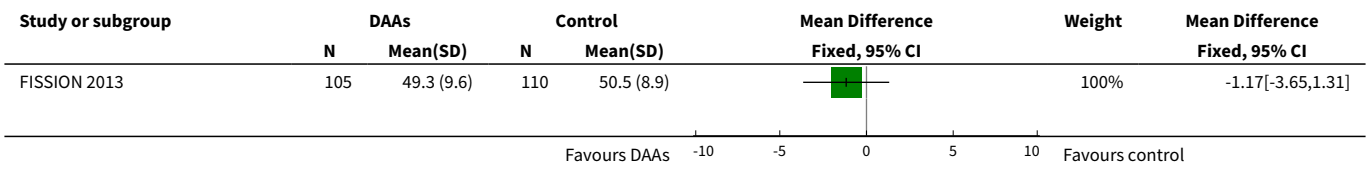
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Rodriguez-Torres 2014a4	0/10	1/2		0.11%	0.09[0,1.71]
Sullivan 2012	14/28	7/9		1.15%	0.64[0.39,1.07]
Tanwandee 2012	1/15	2/8		0.18%	0.27[0.03,2.51]
Tatum 2015a1	4/13	4/7		0.59%	0.54[0.19,1.52]
Tatum 2015a2	8/13	4/6		0.9%	0.92[0.45,1.88]
Wedemeyer 2013	183/324	39/84		1.5%	1.22[0.95,1.56]
Subtotal (95% CI)	**5194**	**1692**		**46.17%**	**0.44[0.37,0.52]**
Total events: 1180 (DAAs), 915 (Control)					
Heterogeneity: Tau²=0.27; Chi²=266.16, df=59(P<0.0001); I²=77.83%					
Test for overall effect: Z=9.19(P<0.0001)					
7.1.2 Trials assessing DAAs withdrawn from market					
ADVANCE 2011a1	92/363	101/180		1.53%	0.45[0.36,0.56]
ADVANCE 2011a2	114/364	102/181		1.55%	0.56[0.46,0.68]
Bacon 2011a1	67/162	32/40		1.5%	0.52[0.41,0.66]
Bacon 2011a2	54/161	31/40		1.47%	0.43[0.33,0.57]
Benhamou 2013a1	3/8	1/4		0.23%	1.5[0.22,10.22]
Benhamou 2013a2	4/8	2/4		0.48%	1[0.3,3.32]
Flamm 2013	48/134	53/67		1.48%	0.45[0.35,0.59]
Foster 2011a1	3/14	3/9		0.4%	0.64[0.16,2.51]
Foster 2011a2	8/17	3/9		0.58%	1.41[0.49,4.04]
Hezode 2009	108/241	44/82		1.5%	0.84[0.65,1.07]
Kwo 2010a1	45/103	17/26		1.36%	0.67[0.47,0.95]
Kwo 2010a2	26/103	16/26		1.23%	0.41[0.26,0.64]
Kwo 2010a3	49/107	16/26		1.35%	0.74[0.52,1.07]
Kwo 2010a4	34/103	16/26		1.29%	0.54[0.36,0.81]
Lawitz 2011b	84/188	28/64		1.41%	1.02[0.74,1.41]
Manns 2011	14/26	8/8		1.32%	0.57[0.39,0.84]
McHutchison 2009	68/175	44/75		1.48%	0.66[0.51,0.86]
McHutchison 2010	193/339	98/114		1.61%	0.66[0.59,0.75]
Nelson 2012a1	24/74	4/12		0.73%	0.97[0.41,2.31]
Nelson 2012a2	27/70	5/12		0.87%	0.93[0.45,1.92]
Nelson 2012a3	40/72	5/12		0.91%	1.33[0.66,2.69]
Nelson 2012a4	33/71	5/12		0.89%	1.12[0.55,2.28]
Nelson 2012a5	37/70	5/12		0.9%	1.27[0.63,2.57]
Nelson 2012a6	30/75	5/12		0.88%	0.96[0.47,1.98]
Nishiguchi 2014a1	2/6	1/2		0.26%	0.67[0.11,3.99]
Nishiguchi 2014a2	1/6	1/2		0.17%	0.33[0.03,3.2]
Pearlman 2014	5/49	6/52		0.53%	0.88[0.29,2.71]
Pol 2013	46/178	36/61		1.4%	0.44[0.32,0.61]
Poordad 2011a1	135/368	113/182		1.57%	0.59[0.5,0.7]
Poordad 2011a2	124/366	113/181		1.56%	0.54[0.45,0.65]
Rodriguez-Torres 2014b1	31/71	16/38		1.22%	1.04[0.66,1.64]
Rodriguez-Torres 2014b2	36/74	16/38		1.25%	1.16[0.74,1.79]
STARTVerso-1 2015a1	55/259	31/66		1.37%	0.45[0.32,0.64]
STARTVerso-1 2015a2	51/261	32/66		1.37%	0.4[0.28,0.57]
STARTverso-2 2014a1	54/259	31/66		1.37%	0.44[0.31,0.63]
STARTverso-2 2014a2	53/261	32/66		1.38%	0.42[0.3,0.59]
STARTverso-3 2013a1	57/156	35/39		1.51%	0.41[0.32,0.51]
STARTverso-3 2013a2	64/158	35/39		1.53%	0.45[0.36,0.56]
STARTverso-3 2013a3	94/140	96/145		1.58%	1.01[0.86,1.2]
STARTverso-4 2015	22/86	18/84		1.1%	1.19[0.69,2.06]

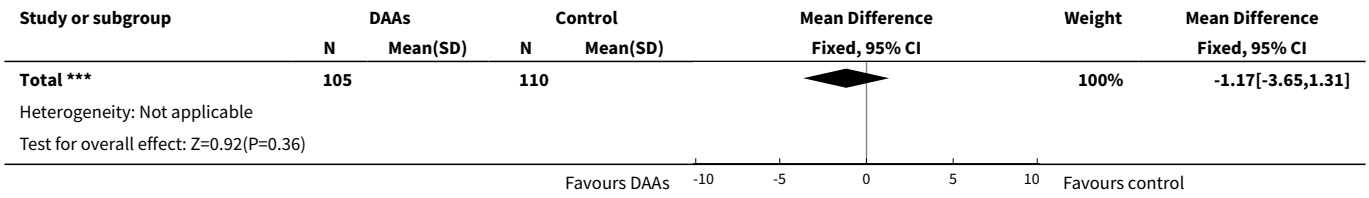


Comparison 8. All DAA versus placebo/no intervention/other medical intervention (quality of life scores)

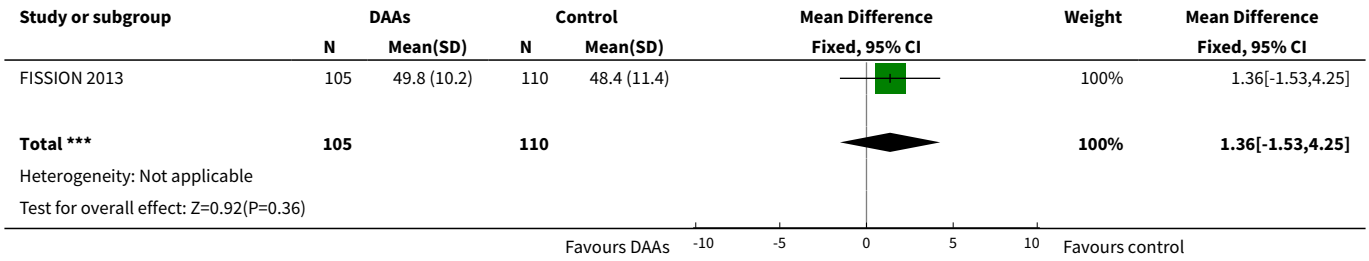
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SF-36 physical score	1	215	Mean Difference (IV, Fixed, 95% CI)	-1.17 [-3.65, 1.31]
2 SF-36 mental score	1	215	Mean Difference (IV, Fixed, 95% CI)	1.36 [-1.53, 4.25]

Analysis 8.1. Comparison 8 All DAA versus placebo/no intervention/other medical intervention (quality of life scores), Outcome 1 SF-36 physical score.





Analysis 8.2. Comparison 8 All DAA versus placebo/no intervention/other medical intervention (quality of life scores), Outcome 2 SF-36 mental score.



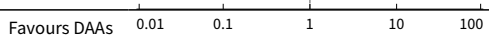
Comparison 9. Daclatasvir versus placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hepatitis C-related morbidity or all-cause mortality	14	666	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.06, 26.65]
2 Hepatitis C-related morbidity or all-cause mortality - according to dose	14	666	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.06, 26.65]
2.1 Over or equal to median dose	7	374	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Under median dose	7	292	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.06, 26.65]
2.3 Not available	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Serious adverse events	13		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Serious adverse events - according to median dose	14		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Over or equal to median dose	7		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Under median dose	8		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 Not available	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Without sustained virological response	7	619	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.27, 0.59]
6 Without sustained virological response - according to median dose	7	619	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.27, 0.59]
6.1 Over or equal to median dose	4	360	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.26, 0.70]
6.2 Under median dose	3	259	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.19, 0.68]
6.3 Not available	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 9.1. Comparison 9 Daclatasvir versus placebo/no intervention, Outcome 1 Hepatitis C-related morbidity or all-cause mortality.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
COMMAND-1 2015a1	2/159	0/39		100%	1.25[0.06,26.65]
COMMAND-1 2015a2	0/158	0/39			Not estimable
Dore 2015a1	0/50	0/25			Not estimable
Dore 2015a2	0/50	0/25			Not estimable
Izumi 2014a1	0/9	0/4			Not estimable
Izumi 2014a2	0/8	0/4			Not estimable
Nettles 2010	0/16	0/2			Not estimable
Nettles 2011a1	0/4	0/1			Not estimable
Nettles 2011a2	0/4	0/1			Not estimable
Nettles 2011a3	0/4	0/1			Not estimable
Nettles 2011a4	0/4	0/1			Not estimable
Nettles 2011a5	0/4	0/1			Not estimable
Nettles 2011a6	0/4	0/1			Not estimable
Pol 2012	0/36	0/12			Not estimable
Total (95% CI)	**510**	**156**		**100%**	**1.25[0.06,26.65]**
Total events: 2 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.15(P=0.88)					

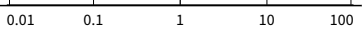


Analysis 9.2. Comparison 9 Daclatasvir versus placebo/no intervention, Outcome 2 Hepatitis C-related morbidity or all-cause mortality - according to dose.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
9.2.1 Over or equal to median dose					
COMMAND-1 2015a2	0/158	0/39			Not estimable
Dore 2015a1	0/50	0/25			Not estimable
Dore 2015a2	0/50	0/25			Not estimable
Izumi 2014a2	0/8	0/4			Not estimable
Nettles 2011a3	0/4	0/1			Not estimable
Nettles 2011a5	0/4	0/1			Not estimable
Nettles 2011a6	0/4	0/1			Not estimable
Subtotal (95% CI)	**278**	**96**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.2.2 Under median dose					
COMMAND-1 2015a1	2/159	0/39		100%	1.25[0.06,26.65]
Izumi 2014a1	0/9	0/4			Not estimable
Nettles 2010	0/16	0/2			Not estimable
Nettles 2011a1	0/4	0/1			Not estimable
Nettles 2011a2	0/4	0/1			Not estimable
Nettles 2011a4	0/4	0/1			Not estimable
Pol 2012	0/36	0/12			Not estimable
Subtotal (95% CI)	**232**	**60**		**100%**	**1.25[0.06,26.65]**
Total events: 2 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.15(P=0.88)					
9.2.3 Not available					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**510**	**156**		**100%**	**1.25[0.06,26.65]**
Total events: 2 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.15(P=0.88)					
Test for subgroup differences: Not applicable					

Analysis 9.3. Comparison 9 Daclatasvir versus placebo/no intervention, Outcome 3 Serious adverse events.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
Pol 2012	3/36	0/12		2.61[0.13,54.25]

Favours DAAs 0.01 0.1 1 10 100 Favours control

Analysis 9.4. Comparison 9 Daclatasvir versus placebo/no intervention, Outcome 4 Serious adverse events - according to median dose.

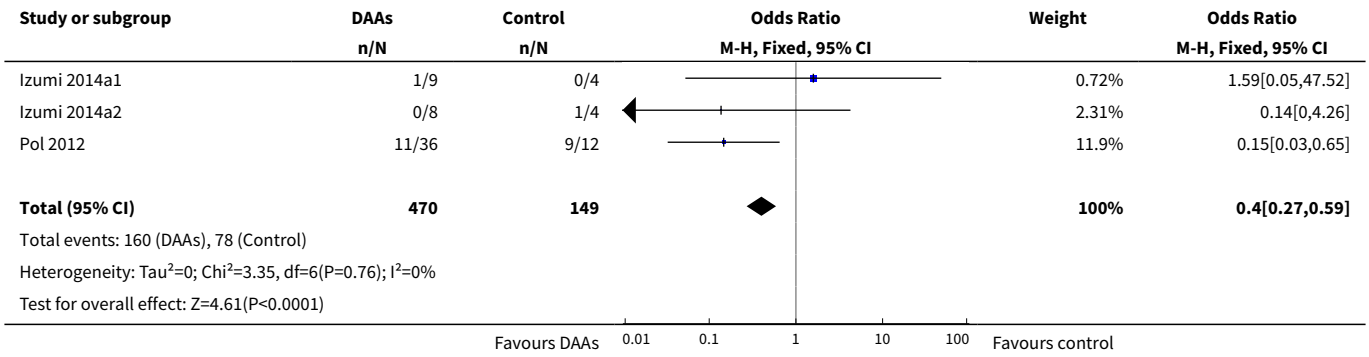
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
9.4.1 Over or equal to median dose				
COMMAND-1 2015a2	13/158	3/39		1.08[0.29,3.98]
Dore 2015a1	4/50	2/25		1[0.17,5.87]
Dore 2015a2	0/50	1/26		0.17[0.01,4.28]
Izumi 2014a2	0/8	0/4		Not estimable
Nettles 2011a3	0/4	0/1		Not estimable
Nettles 2011a5	0/4	0/1		Not estimable
Nettles 2011a6	0/4	0/1		Not estimable
9.4.2 Under median dose				
COMMAND-1 2015a1	12/159	3/39		0.98[0.26,3.65]
Izumi 2014a1	2/9	0/4		3[0.12,77.64]
Izumi 2014a2	0/8	0/4		Not estimable
Nettles 2010	0/16	0/2		Not estimable
Nettles 2011a1	0/4	0/1		Not estimable
Nettles 2011a2	0/4	0/1		Not estimable
Nettles 2011a4	0/4	0/1		Not estimable
Pol 2012	3/36	0/12		2.61[0.13,54.25]
9.4.3 Not available				

Favours DAAs 0.01 0.1 1 10 100 Favours control

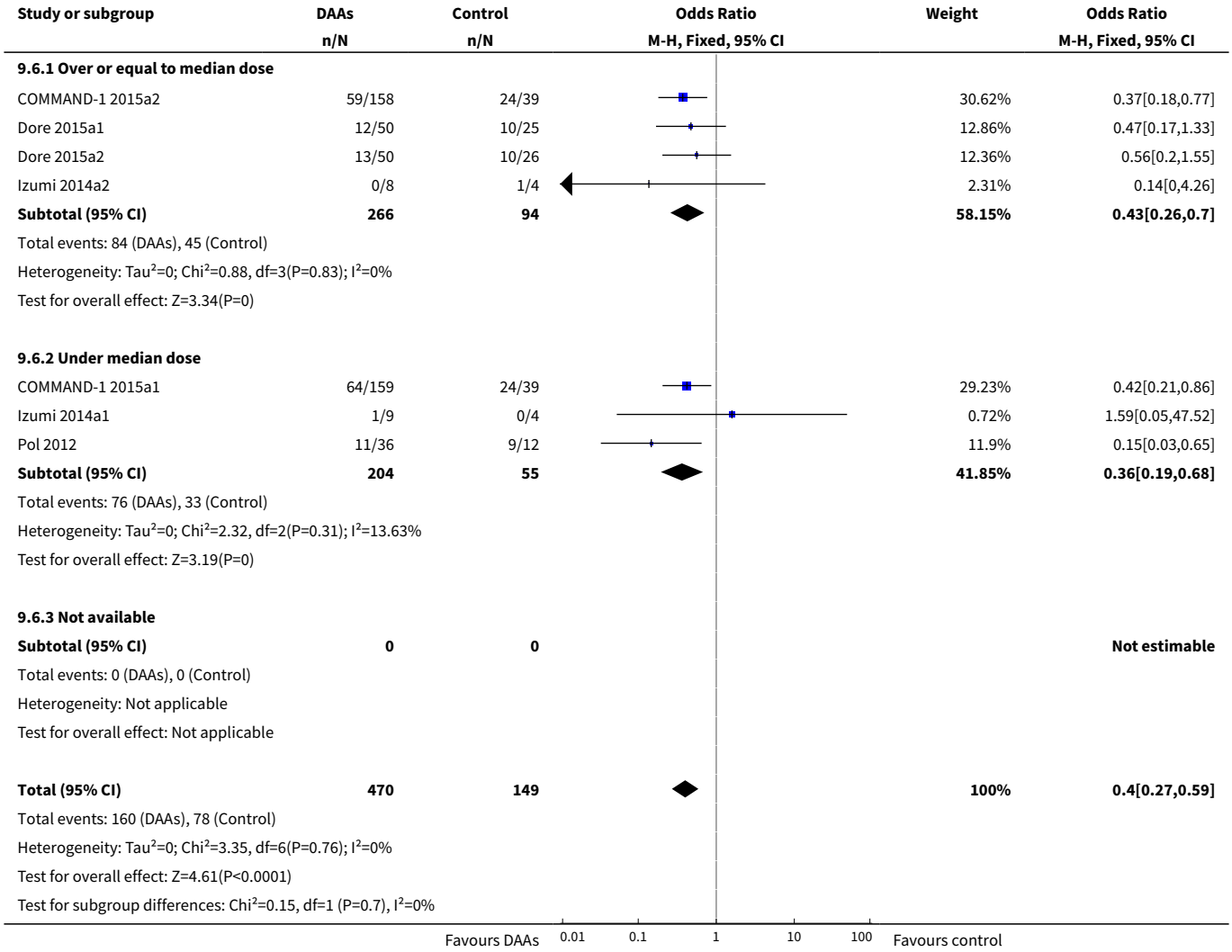
Analysis 9.5. Comparison 9 Daclatasvir versus placebo/no intervention, Outcome 5 Without sustained virological response.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
COMMAND-1 2015a1	64/159	24/39		29.23%	0.42[0.21,0.86]
COMMAND-1 2015a2	59/158	24/39		30.62%	0.37[0.18,0.77]
Dore 2015a1	12/50	10/25		12.86%	0.47[0.17,1.33]
Dore 2015a2	13/50	10/26		12.36%	0.56[0.2,1.55]

Favours DAAs 0.01 0.1 1 10 100 Favours control



Analysis 9.6. Comparison 9 Daclatasvir versus placebo/no intervention, Outcome 6 Without sustained virological response - according to median dose.

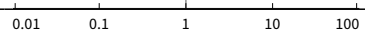


Comparison 10. Simeprevir versus placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hepatitis C-related morbidity or all-cause mortality	14	1589	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.08, 2.96]
2 Hepatitis C-related morbidity or all-cause mortality - according to dose	14	1589	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.08, 2.96]
2.1 Over or equal to median dose	4	441	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.03, 8.21]
2.2 Under median dose	8	705	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.01, 12.22]
2.3 Not available	2	443	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.02, 13.62]
3 Serious adverse events	18		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Serious adverse events - according to median dose	18		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Over or equal to median dose	7		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Under median dose	9		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Not available	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Without sustained virological response	19	2898	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.19, 0.27]
6 Without sustained virological response - according to median dose	19	2898	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.19, 0.27]
6.1 Over or equal to median dose	9	1765	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.20, 0.32]
6.2 Under median dose	8	696	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.13, 0.29]
6.3 Not available	2	437	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.07, 0.24]

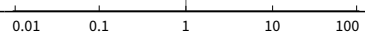
Analysis 10.1. Comparison 10 Simeprevir versus placebo/no intervention, Outcome 1 Hepatitis C-related morbidity or all-cause mortality.

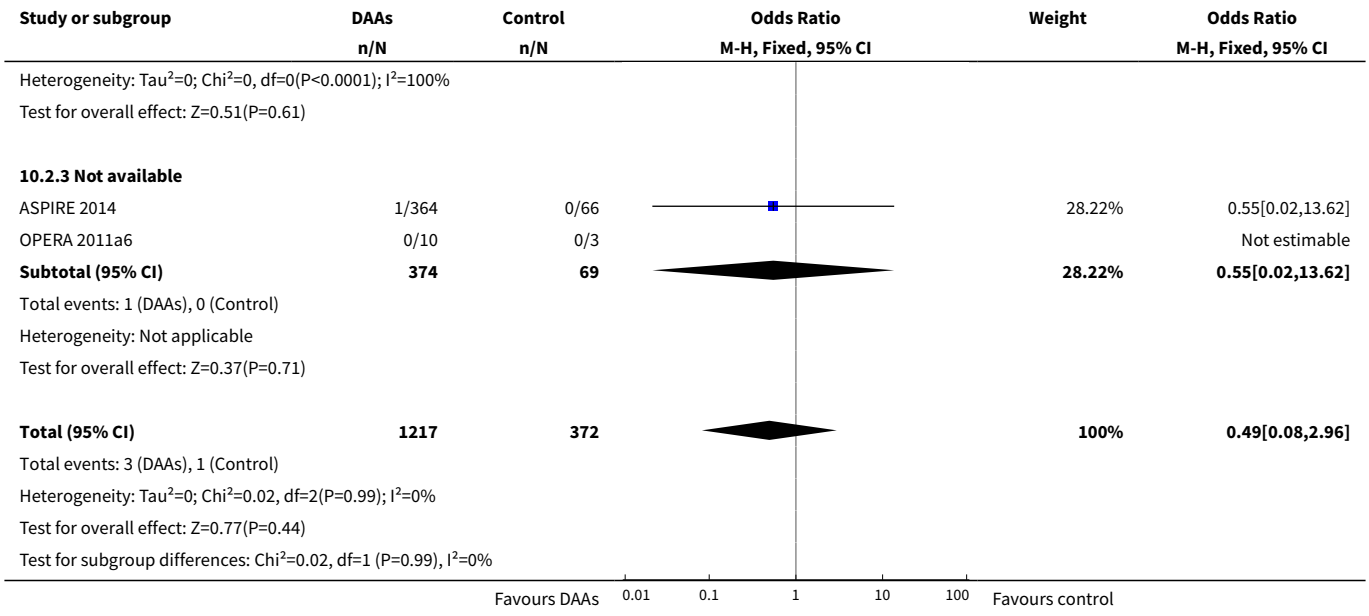
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
ASPIRE 2014	1/364	0/66		28.22%	0.55[0.02,13.62]
CONCERTO-1 2015	0/123	0/60			Not estimable
DRAGON 2014a1	0/27	0/3			Not estimable
DRAGON 2014a2	0/13	0/3			Not estimable
DRAGON 2014a3	1/26	0/3		27.58%	0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4			Not estimable
Forns 2014	1/260	1/133		44.2%	0.51[0.03,8.21]
Fried 2013	0/309	0/77			Not estimable
OPERA 2011a1	0/18	0/4			Not estimable
OPERA 2011a2	0/19	0/3			Not estimable
OPERA 2011a3	0/18	0/6			Not estimable
OPERA 2011a4	0/9	0/4			Not estimable
OPERA 2011a5	0/8	0/3			Not estimable
OPERA 2011a6	0/10	0/3			Not estimable
Total (95% CI)	**1217**	**372**		**100%**	**0.49[0.08,2.96]**
Total events: 3 (DAAs), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=2(P=0.99); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					



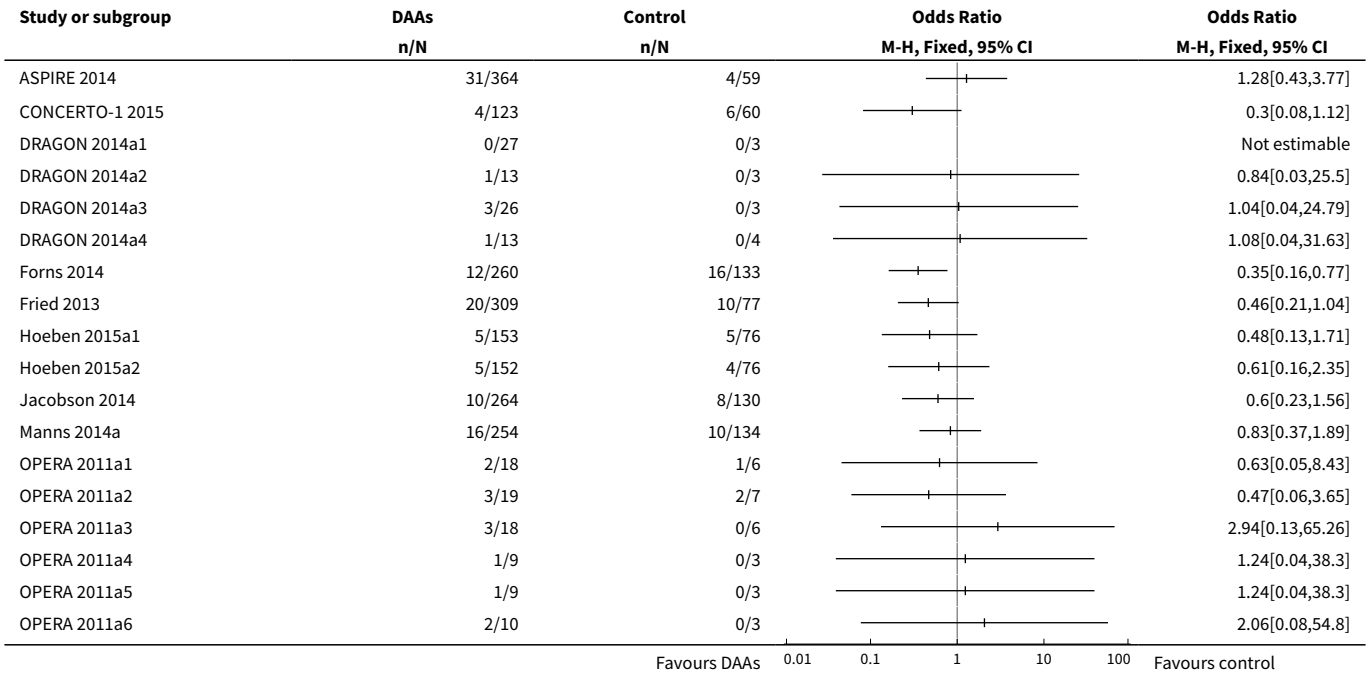
Analysis 10.2. Comparison 10 Simeprevir versus placebo/no intervention, Outcome 2 Hepatitis C-related morbidity or all-cause mortality - according to dose.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
10.2.1 Over or equal to median dose					
Forns 2014	1/260	1/133		44.2%	0.51[0.03,8.21]
OPERA 2011a3	0/18	0/6			Not estimable
OPERA 2011a4	0/9	0/4			Not estimable
OPERA 2011a5	0/8	0/3			Not estimable
Subtotal (95% CI)	**295**	**146**		**44.2%**	**0.51[0.03,8.21]**
Total events: 1 (DAAs), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.48(P=0.63)					
10.2.2 Under median dose					
CONCERTO-1 2015	0/123	0/60			Not estimable
DRAGON 2014a1	0/27	0/3			Not estimable
DRAGON 2014a2	0/13	0/3			Not estimable
DRAGON 2014a3	1/26	0/3		27.58%	0.41[0.01,12.22]
DRAGON 2014a4	0/13	0/4			Not estimable
Fried 2013	0/309	0/77			Not estimable
OPERA 2011a1	0/18	0/4			Not estimable
OPERA 2011a2	0/19	0/3			Not estimable
Subtotal (95% CI)	**548**	**157**		**27.58%**	**0.41[0.01,12.22]**
Total events: 1 (DAAs), 0 (Control)					



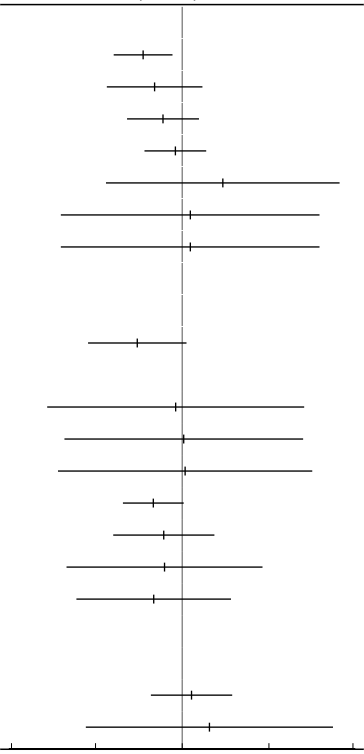


Analysis 10.3. Comparison 10 Simeprevir versus placebo/no intervention, Outcome 3 Serious adverse events.



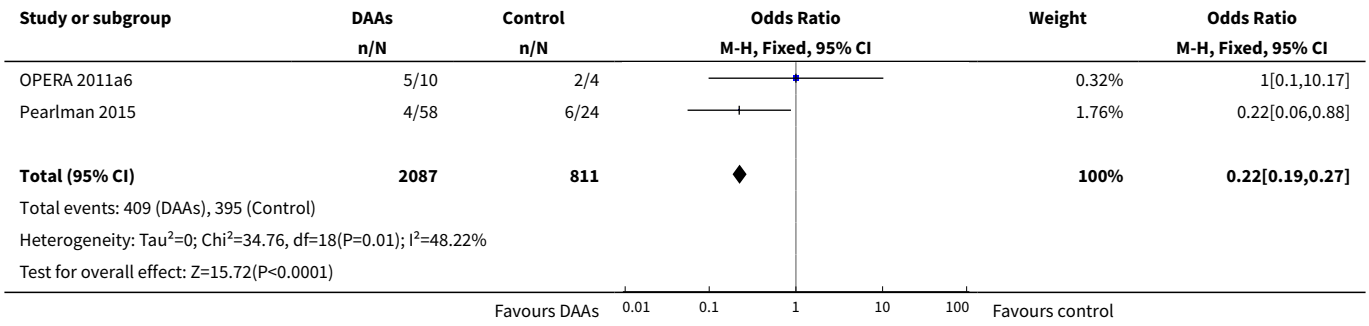
Analysis 10.4. Comparison 10 Simeprevir versus placebo/no intervention, Outcome 4 Serious adverse events - according to median dose.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
10.4.1 Over or equal to median dose				
Forns 2014	12/260	16/133		0.35[0.16,0.77]
Hoeben 2015a1	5/153	5/76		0.48[0.13,1.71]
Jacobson 2014	10/264	8/130		0.6[0.23,1.56]
Manns 2014a	16/254	10/134		0.83[0.37,1.89]
OPERA 2011a3	3/18	0/6		2.94[0.13,65.26]
OPERA 2011a4	1/9	0/3		1.24[0.04,38.3]
OPERA 2011a5	1/9	0/3		1.24[0.04,38.3]
10.4.2 Under median dose				
CONCERTO-1 2015	4/123	6/60		0.3[0.08,1.12]
DRAGON 2014a1	0/27	0/3		Not estimable
DRAGON 2014a2	1/13	0/3		0.84[0.03,25.5]
DRAGON 2014a3	3/26	0/3		1.04[0.04,24.79]
DRAGON 2014a4	1/13	0/4		1.08[0.04,31.63]
Fried 2013	20/309	10/77		0.46[0.21,1.04]
Hoeben 2015a2	5/152	4/76		0.61[0.16,2.35]
OPERA 2011a1	2/18	1/6		0.63[0.05,8.43]
OPERA 2011a2	3/19	2/7		0.47[0.06,3.65]
10.4.3 Not available				
ASPIRE 2014	31/364	4/59		1.28[0.43,3.77]
OPERA 2011a6	2/10	0/3		2.06[0.08,54.8]

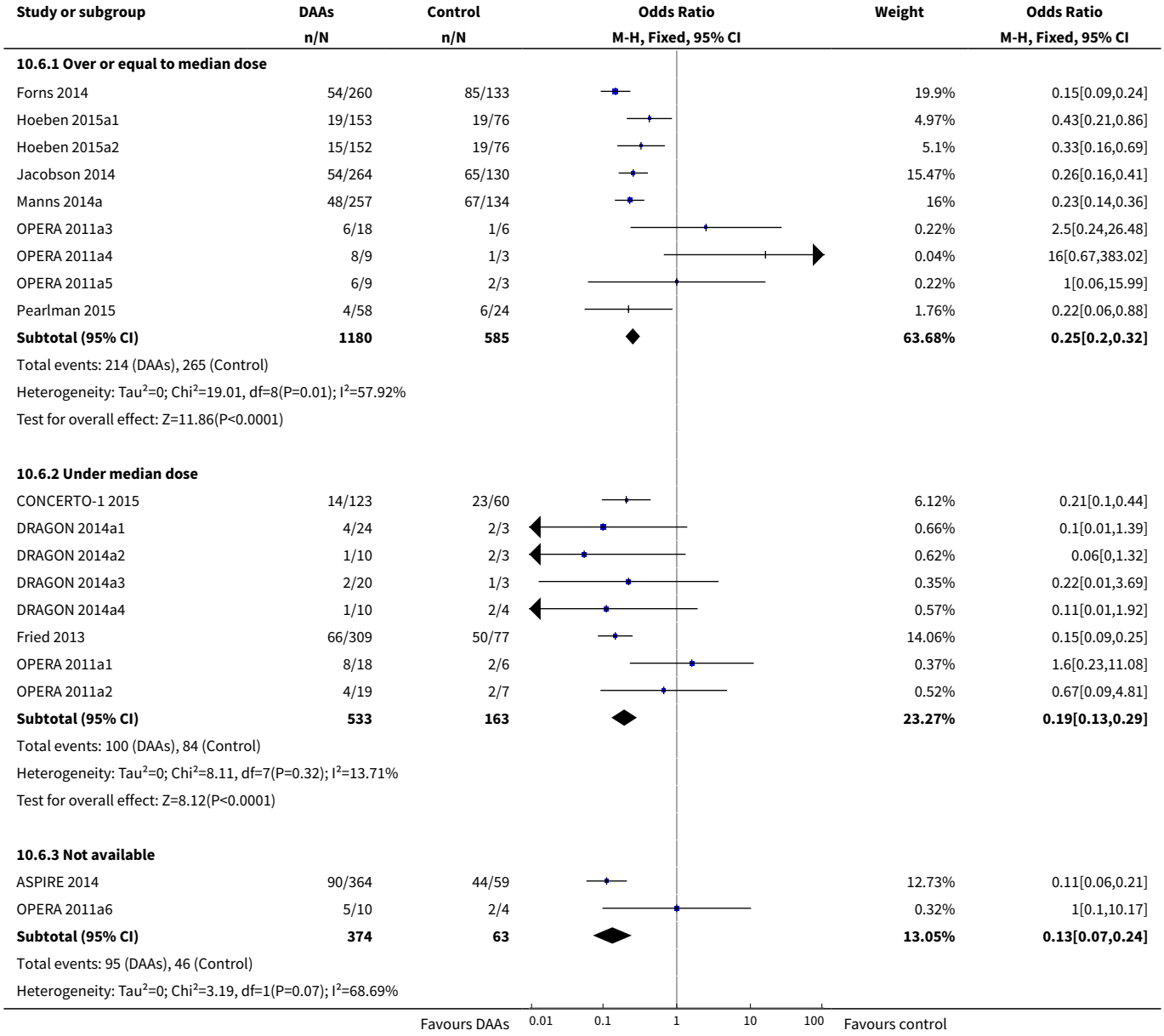


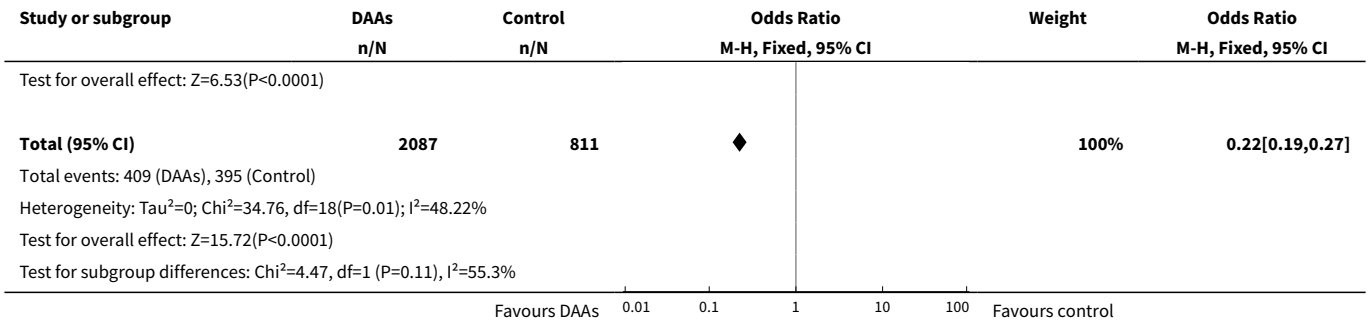
Analysis 10.5. Comparison 10 Simeprevir versus placebo/no intervention, Outcome 5 Without sustained virological response.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
ASPIRE 2014	90/364	44/59		12.73%	0.11[0.06,0.21]
CONCERTO-1 2015	14/123	23/60		6.12%	0.21[0.1,0.44]
DRAGON 2014a1	4/24	2/3		0.66%	0.1[0.01,1.39]
DRAGON 2014a2	1/10	2/3		0.62%	0.06[0,1.32]
DRAGON 2014a3	2/20	1/3		0.35%	0.22[0.01,3.69]
DRAGON 2014a4	1/10	2/4		0.57%	0.11[0.01,1.92]
Forns 2014	54/260	85/133		19.9%	0.15[0.09,0.24]
Fried 2013	66/309	50/77		14.06%	0.15[0.09,0.25]
Hoeben 2015a1	19/153	19/76		4.97%	0.43[0.21,0.86]
Hoeben 2015a2	15/152	19/76		5.1%	0.33[0.16,0.69]
Jacobson 2014	54/264	65/130		15.47%	0.26[0.16,0.41]
Manns 2014a	48/257	67/134		16%	0.23[0.14,0.36]
OPERA 2011a1	8/18	2/6		0.37%	1.6[0.23,11.08]
OPERA 2011a2	4/19	2/7		0.52%	0.67[0.09,4.81]
OPERA 2011a3	6/18	1/6		0.22%	2.5[0.24,26.48]
OPERA 2011a4	8/9	1/3		0.04%	16[0.67,383.02]
OPERA 2011a5	6/9	2/3		0.22%	1[0.06,15.99]



Analysis 10.6. Comparison 10 Simeprevir versus placebo/no intervention, Outcome 6 Without sustained virological response - according to median dose.





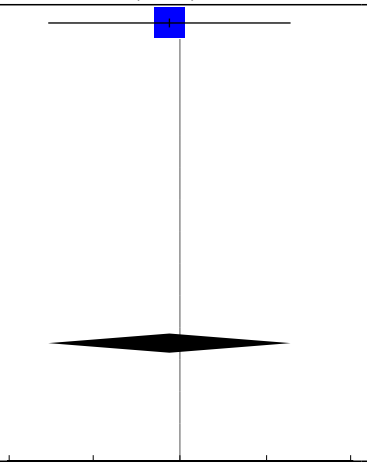
Comparison 11. Vaniprevir versus placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hepatitis C-related morbidity or all-cause mortality	9	379	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.03, 18.90]
2 Hepatitis C-related morbidity or all-cause mortality - according to dose	9	379	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.03, 18.90]
2.1 Over or equal to median dose	6	313	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.03, 18.90]
2.2 Under median dose	3	66	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Not available	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Serious adverse events	10		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Serious adverse events - according to median dose	10		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Over or equal to median dose	6		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Under median dose	4		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Not available	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Without sustained virological response	9	333	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.06, 0.22]
6 Without sustained virological response - according to median dose	9	333	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.06, 0.22]
6.1 Over or equal to median dose	6	280	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.05, 0.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Under median dose	3	53	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.06, 1.04]
6.3 Not available	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

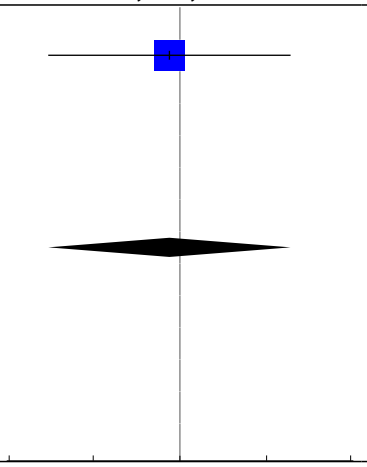
Analysis 11.1. Comparison 11 Vaniprevir versus placebo/no intervention, Outcome 1 Hepatitis C-related morbidity or all-cause mortality.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2013c	1/169	0/42		100%	0.76[0.03,18.9]
Manns 2012a1	0/18	0/5			Not estimable
Manns 2012a2	0/20	0/5			Not estimable
Manns 2012a3	0/18	0/5			Not estimable
Manns 2012a4	0/19	0/4			Not estimable
Rodriguez-Torres 2014a1	0/16	0/4			Not estimable
Rodriguez-Torres 2014a2	0/14	0/3			Not estimable
Rodriguez-Torres 2014a3	0/15	0/4			Not estimable
Rodriguez-Torres 2014a4	0/15	0/3			Not estimable
Total (95% CI)	**304**	**75**		**100%**	**0.76[0.03,18.9]**
Total events: 1 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.87)					



Analysis 11.2. Comparison 11 Vaniprevir versus placebo/no intervention, Outcome 2 Hepatitis C-related morbidity or all-cause mortality - according to dose.

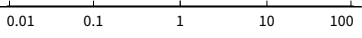
Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
11.2.1 Over or equal to median dose					
Lawitz 2013c	1/169	0/42		100%	0.76[0.03,18.9]
Manns 2012a2	0/20	0/5			Not estimable
Manns 2012a4	0/19	0/4			Not estimable
Rodriguez-Torres 2014a2	0/14	0/3			Not estimable
Rodriguez-Torres 2014a3	0/15	0/4			Not estimable
Rodriguez-Torres 2014a4	0/15	0/3			Not estimable
Subtotal (95% CI)	**252**	**61**		**100%**	**0.76[0.03,18.9]**
Total events: 1 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.87)					
11.2.2 Under median dose					
Manns 2012a1	0/18	0/5			Not estimable



Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Manns 2012a3	0/18	0/5			Not estimable
Rodriguez-Torres 2014a1	0/16	0/4			Not estimable
Subtotal (95% CI)	**52**	**14**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
11.2.3 Not available					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**304**	**75**		**100%**	**0.76[0.03,18.9]**
Total events: 1 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.87)					
Test for subgroup differences: Not applicable					

Analysis 11.3. Comparison 11 Vaniprevir versus placebo/no intervention, Outcome 3 Serious adverse events.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Lawitz 2013e	0/35	0/5		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]



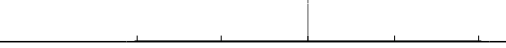
Analysis 11.4. Comparison 11 Vaniprevir versus placebo/no intervention, Outcome 4 Serious adverse events - according to median dose.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
11.4.1 Over or equal to median dose				
Lawitz 2013c	19/169	0/42		11.01[0.65,186.19]
Manns 2012a2	1/20	0/5		0.85[0.03,23.82]
Manns 2012a4	2/19	0/4		1.29[0.05,31.8]
Rodriguez-Torres 2014a1	2/16	1/4		0.43[0.03,6.41]
Rodriguez-Torres 2014a2	0/14	0/3		Not estimable

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Rodriguez-Torres 2014a3	0/15	0/4		Not estimable
11.4.2 Under median dose				
Lawitz 2013e	0/35	0/5		Not estimable
Manns 2012a1	3/18	1/5		0.8[0.06,9.92]
Manns 2012a3	2/18	0/5		1.67[0.07,40.32]
Rodriguez-Torres 2014a4	1/15	0/3		0.72[0.02,21.85]
11.4.3 Not available				

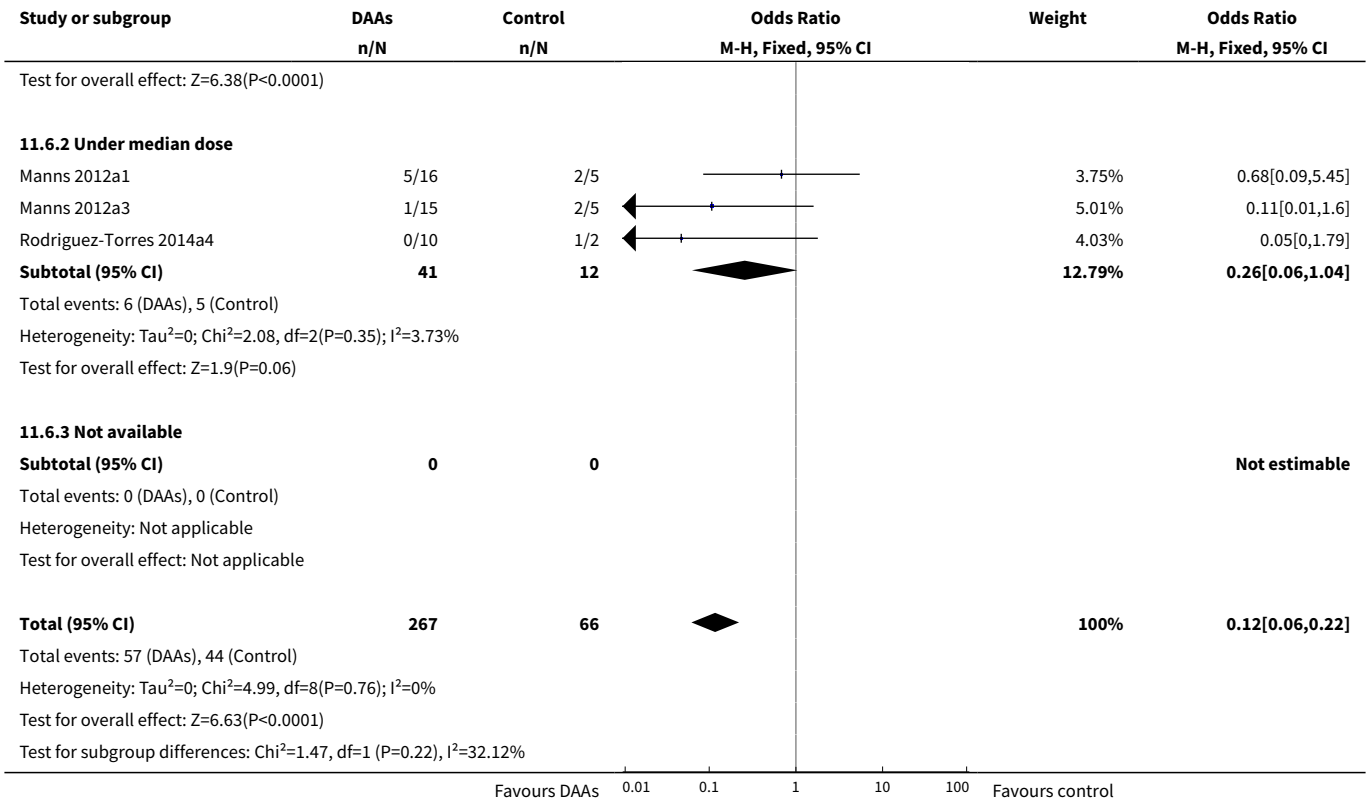
Analysis 11.5. Comparison 11 Vaniprevir versus placebo/no intervention, Outcome 5 Without sustained virological response.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Lawitz 2013c	39/156	34/42		71.91%	0.08[0.03,0.18]
Manns 2012a1	5/16	2/5		3.75%	0.68[0.09,5.45]
Manns 2012a2	1/17	1/4		2.73%	0.19[0.01,3.9]
Manns 2012a3	1/15	2/5		5.01%	0.11[0.01,1.6]
Manns 2012a4	2/18	1/4		2.6%	0.38[0.03,5.57]
Rodriguez-Torres 2014a1	5/14	1/1		3%	0.19[0.01,5.6]
Rodriguez-Torres 2014a2	0/9	1/2		3.92%	0.05[0,1.99]
Rodriguez-Torres 2014a3	4/12	1/1		3.04%	0.18[0.01,5.28]
Rodriguez-Torres 2014a4	0/10	1/2		4.03%	0.05[0,1.79]
Total (95% CI)	**267**	**66**		**100%**	**0.12[0.06,0.22]**
Total events: 57 (DAAs), 44 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.99, df=8(P=0.76); I^2=0%					
Test for overall effect: Z=6.63(P<0.0001)					



Analysis 11.6. Comparison 11 Vaniprevir versus placebo/no intervention, Outcome 6 Without sustained virological response - according to median dose.

Study or subgroup	DAAs n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
11.6.1 Over or equal to median dose					
Lawitz 2013c	39/156	34/42		71.91%	0.08[0.03,0.18]
Manns 2012a2	1/17	1/4		2.73%	0.19[0.01,3.9]
Manns 2012a4	2/18	1/4		2.6%	0.38[0.03,5.57]
Rodriguez-Torres 2014a1	5/14	1/1		3%	0.19[0.01,5.6]
Rodriguez-Torres 2014a2	0/9	1/2		3.92%	0.05[0,1.99]
Rodriguez-Torres 2014a3	4/12	1/1		3.04%	0.18[0.01,5.28]
Subtotal (95% CI)	**226**	**54**		**87.21%**	**0.1[0.05,0.2]**
Total events: 51 (DAAs), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.77, df=5(P=0.88); I^2=0%					

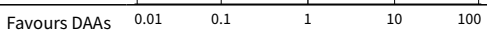


Comparison 12. All DAA versus placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Without significant reductions in ALT/AST serum levels	11	2099	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.68, 0.92]
2 Without significant reductions in ALT/AST serum levels - according to DAA status	11	2099	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.68, 0.92]
2.1 Trials assessing DAAs on or on the way to the market	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Trials assessing DAAs withdrawn from market	11	2099	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.68, 0.92]
3 Without significant reductions in ALT/AST serum levels - according to type of drug	11	2099	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.68, 0.92]
3.1 Faldaprevir	8	2019	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.69, 0.96]
3.2 Balaparavir	3	80	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.41, 0.92]

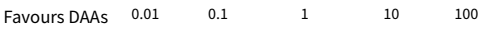
Analysis 12.1. Comparison 12 All DAA versus placebo/no intervention, Outcome 1 Without significant reductions in ALT/AST serum levels.

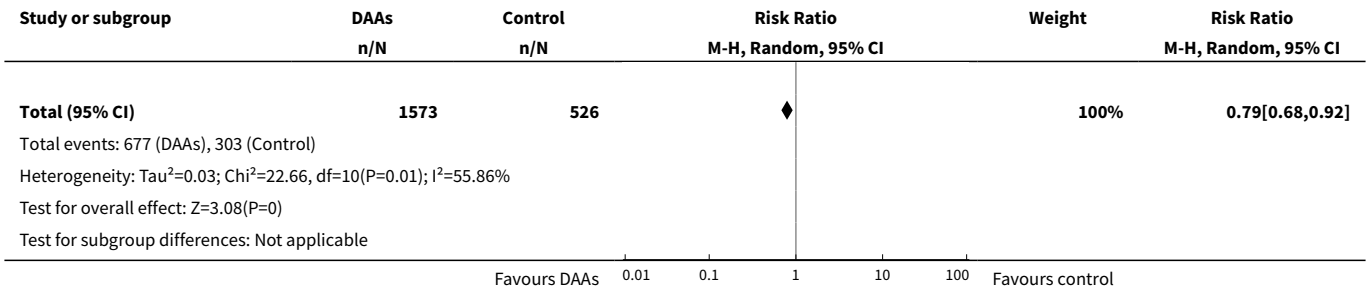
Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pockros 2008a1	7/13	4/5		4.01%	0.67[0.35,1.31]
Pockros 2008a2	11/27	4/5		4.37%	0.51[0.27,0.96]
Pockros 2008a3	11/25	3/5		2.74%	0.73[0.32,1.7]
STARTVerso-1 2015a1	112/230	20/39		9.87%	0.95[0.68,1.33]
STARTVerso-1 2015a2	110/226	19/39		9.44%	1[0.7,1.42]
STARTverso-2 2014a1	37/259	22/66		6.99%	0.43[0.27,0.67]
STARTverso-2 2014a2	45/261	22/66		7.41%	0.52[0.34,0.8]
STARTverso-3 2013a1	103/156	29/39		13.76%	0.89[0.72,1.1]
STARTverso-3 2013a2	111/157	29/38		14.2%	0.93[0.76,1.14]
STARTverso-3 2013a3	92/140	99/144		15.69%	0.96[0.81,1.12]
STARTverso-4 2015	38/79	52/80		11.53%	0.74[0.56,0.98]
Total (95% CI)	**1573**	**526**		**100%**	**0.79[0.68,0.92]**
Total events: 677 (DAAs), 303 (Control)					
Heterogeneity: Tau²=0.03; Chi²=22.66, df=10(P=0.01); I²=55.86%					
Test for overall effect: Z=3.08(P=0)					



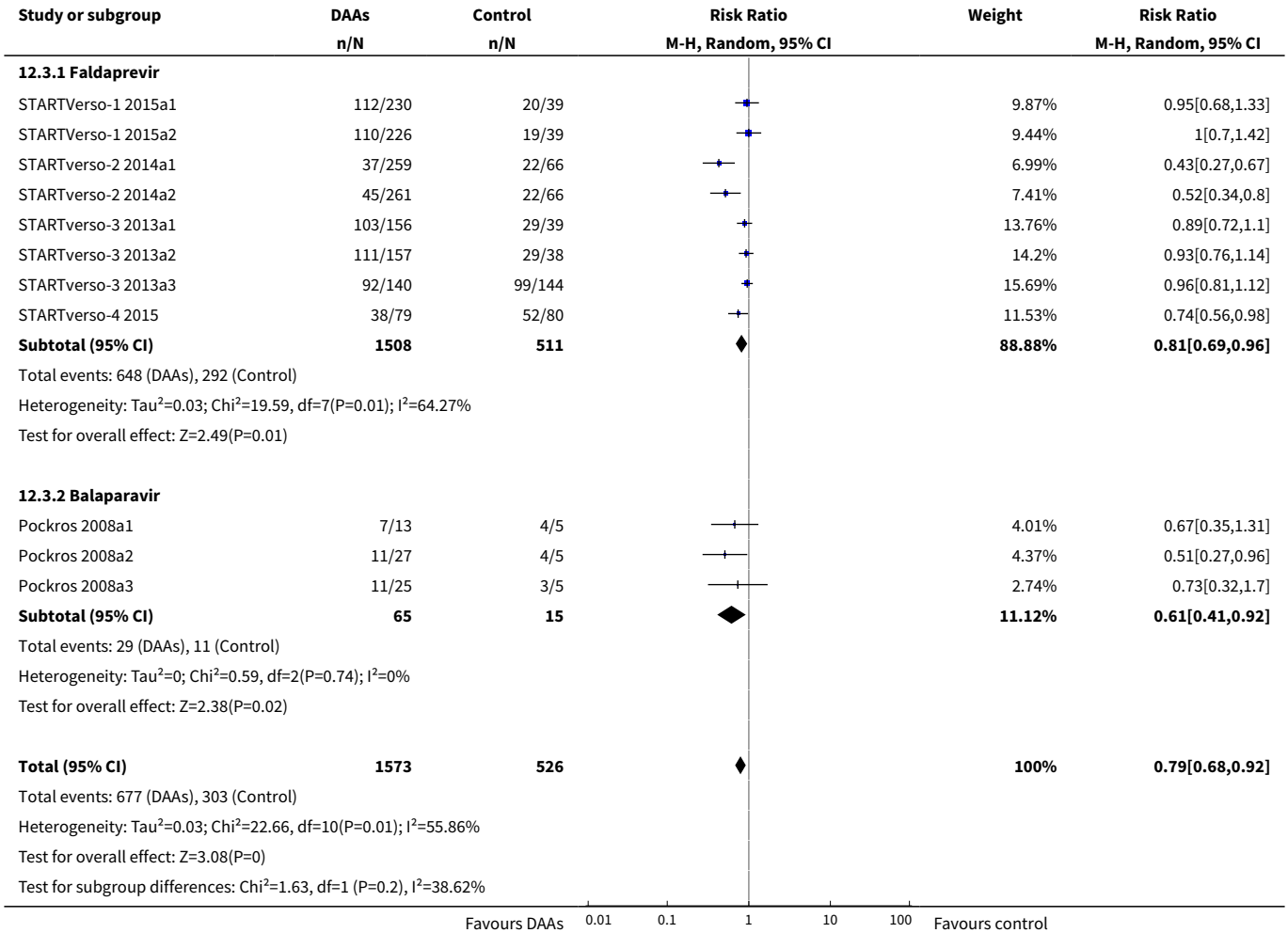
Analysis 12.2. Comparison 12 All DAA versus placebo/no intervention, Outcome 2 Without significant reductions in ALT/AST serum levels - according to DAA status.

Study or subgroup	DAAs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.2.1 Trials assessing DAAs on or on the way to the market					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (DAAs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
12.2.2 Trials assessing DAAs withdrawn from market					
Pockros 2008a1	7/13	4/5		4.01%	0.67[0.35,1.31]
Pockros 2008a2	11/27	4/5		4.37%	0.51[0.27,0.96]
Pockros 2008a3	11/25	3/5		2.74%	0.73[0.32,1.7]
STARTVerso-1 2015a1	112/230	20/39		9.87%	0.95[0.68,1.33]
STARTVerso-1 2015a2	110/226	19/39		9.44%	1[0.7,1.42]
STARTverso-2 2014a1	37/259	22/66		6.99%	0.43[0.27,0.67]
STARTverso-2 2014a2	45/261	22/66		7.41%	0.52[0.34,0.8]
STARTverso-3 2013a1	103/156	29/39		13.76%	0.89[0.72,1.1]
STARTverso-3 2013a2	111/157	29/38		14.2%	0.93[0.76,1.14]
STARTverso-3 2013a3	92/140	99/144		15.69%	0.96[0.81,1.12]
STARTverso-4 2015	38/79	52/80		11.53%	0.74[0.56,0.98]
Subtotal (95% CI)	**1573**	**526**		**100%**	**0.79[0.68,0.92]**
Total events: 677 (DAAs), 303 (Control)					
Heterogeneity: Tau²=0.03; Chi²=22.66, df=10(P=0.01); I²=55.86%					
Test for overall effect: Z=3.08(P=0)					





Analysis 12.3. Comparison 12 All DAA versus placebo/no intervention, Outcome 3 Without significant reductions in ALT/AST serum levels - according to type of drug.



ADDITIONAL TABLES

Table 1. List of direct-acting antivirals

Direct-acting antiviral agents (DAAs)			
NS3/NS4A inhibitors	**NS5B inhibitors**		**NS5A inhibitors**
	NPI	**NNPI**	
ACH-2684	ALS2200/VX135	ABT-072	ACH-2928
Asunaprevir	BILB1941	Beclabuvir	Daclatasvir
Boceprevir	GS0938/PSI352938	BI201127	Elbasvir
Celuprevir	GS6620	Dasabuvir	GSK2336805
Danoprevir	GS9851(PSI7851)	Deleobuvir	Ledipasvir
Faldaprevir	IDX184	Filibuvir	MK-8408
Grazoprevir	INX189/BMS986094	GSK2878175/GSK175	Odalasvir
GS9256	Mericitabine	IDX375	Ombitasvir
GS9857	MK-3682	MK-3281	PPI461
IDX320	Sofosbuvir	Nesbuvir	Ravidasvir
Narlaprevir	VX-135	Radalbuvir	Samatasvir
Paritaprevir	-	Setrobuvir	Velpatasvir
PHX1766	-	Tegobuvir	-
Simperevir	-	TMC-647055	-
Sovaprevir	-	VCH-759	-
Telaprevir	-	VCH-916	-
Vaniprevir	-	VX222	-
Vedroprevir	-	-	-

The table presents a list of 58 direct-acting antiviral agents (DAAs). We have listed the DAAs according to the DAA class they belong to (see Background section). When a DAA has not been assigned a generic or brand name, we have presented it with its experimental compound number prefix.

Table 2. Serious adverse events

Trial	Experimental intervention	Type and number of serious adverse events (experimental group)	Proportion of participants with a serious adverse event (experimental group)	Type and number of serious adverse events (control group)	Proportion of participants with a serious adverse event (control group)

Table 2. Serious adverse events *(Continued)*

Bronowicki 2013a1	Asunaprevir	1 abdominal pain, 1 lung neoplasm malignant, 1 cytolytic hepatitis, and 2 unspecified events	5 out of 36	None reported	0 out of 11
Bronowicki 2014	Asunaprevir	2 deaths and 14 unspecified events	16 out of 177	3 unspecified events	3 out of 61
Nelson 2012a1	Balapiravir	Many events but only a few were specified: 3 deaths, 10 haematological, 10 infection, 8 eye disorders	49 out of 432	Many events but not all were specified: 2 infections, 1 death	9 out of 72
Tatum 2015a1	Beclabuvir	1 anaemia, 1 constipation, 1 febrile neutropenia, 1 leukopenia	1 out of 26	1 serotonin syndrome	1 out of 13
Bacon 2011a1	Boceprevir	5 anaemia, 1 angina pectoris, 1 atrial fibrillation, 1 coronary artery disease, 1 myocardial infarction, 1 myopericarditis, 2 abdominal pain, 1 constipation, 1 diarrhoea, 1 gastritis, 1 irritable bowel syndrome, 1 oesophageal varices haemorrhage, 1 pancreatitis acute, 1 pancreatitis necrotising, 1 peptic ulcer, 1 asthenia, 3 chest pain, 1 oedema peripheral, 1 pyrexia, 1 cholecystitis, 3 appendicitis, 1 bronchopneumonia, 1 catheter site infection, 1 gastroenteritis viral, 1 pneumonia, 1 lower limb fracture, 1 overdose, 1 decreased appetite, 1 dehydration, 1 hyperglycaemia, 1 back pain, 2 intervertebral disc protrusion, 1 pain in extremity, 1 hepatic neoplasm malignant, 1 hepatic encephalopathy, 1 sciatica, 1 syncope, 1 bipolar disorder, 1 completed suicide, 4 depression, 2 homicidal ideation, 5 suicidal ideation, 2 dyspnoea, 1 pleuritic pain, 1 pneumothorax, 1 abdominal hernia repair, 1 deep vein thrombosis, 1 phlebitis	39 out of 323	2 chest pain, 1 cholelithiasis, 1 gastroenteritis	4 out of 80
Flamm 2013	Boceprevir	1 coronary artery disease, 1 diarrhoea, 1 asthenia, 1 pyrexia, 2 pneumonia, 2 syncope, 1 suicidal ideation, 1 deep vein thrombosis, 1 neutropenia, 1 thrombocytopenia, 1 cardiac failure, 1 upper gastrointestinal haemorrhage , 1 multi-organ failure, 1 bronchitis, 1 cellulitis, 1 chlamydia infection, 1 influenza, 1 pneumonia staphylococcal, 1 staphylococcal bacteraemia, 1 staphylococcal infection, 1 urosepsis, 1 gun shot wound, 2 hyponatraemia, 1 lethargy, 1 subarachnoid haemorrhage, 1 mental status changes	18 out of 134	1 chest pain, 1 intervertebral disc protrusion, 1 abnormal behaviour, 1 irritability, 1 osteotomy, 1 foreign body, 1 neuralgia, 1 anxiety, 1 renal colic	7 out of 67
Isakov 2016	Boceprevir	14 neutropenia, 1 intestinal obstruction, 1 osteomyelitis chronic, 1 pneumonia, 1 diabetic ketoacidosis, 1 intervertebral disc protrusion, 1 transient ischaemic attack	17 out of 159	4 neutropenia, 1 general disorders, 1 accidental overdose, 1 prostatitis, 2 hypertension	9 out of 78

Table 2. Serious adverse events *(Continued)*

Kwo 2010a1	Boceprevir	1 anaemia, 1 abdominal pain, 2 asthenia, 2 pyrexia, 2 pneumonia, 1 decreased appetite, 1 dehydration, 2 depression, 2 homicidal ideation, 3 suicidal ideation, 1 dyspnoea, 1 deep vein thrombosis, 3 nausea, 1 vomiting, 3 neutropenia, 1 multi-organ failure, 2 cellulitis, 2 abdominal pain upper, 1 headache, 1 suicide attempt, 1 accidental overdose, 1 fall, 1 pulmonary embolism, 1 gastroenteritis, 1 erysipelas, 1 panic attack, 1 fatigue, 1 supraventricular tachycardia, 3 pancreatitis, 1 cerebrovascular accident, 1 hypoaesthesia, 1 anxiety, 1 retinal ischaemia, 1 neuropathy peripheral, 1 aggression, 1 scotoma, 1 hypovolaemia, 1 vulval abscess, 1 retinopathy, 1 inguinal hernia, 1 cervix carcinoma, 1 pericarditis, 1 paranoia, 1 neutrophil count decreased, 1 paraesthesia, 1 peritoneal haemorrhage, 1 deafness unilateral, 1 periodontal disease, 1 corneal infection, 1 pneumonia streptococcal, 1 drug toxicity, 1 blood amylase increased, 1 lipase increased, 1 basal cell carcinoma, 1 renal cell carcinoma	40 out of 527	1 suicidal ideation, 1 breast cancer, 1 parathyroid tumour benign, 1 muscle spasms, 1 rib fracture, 1 contusion, 1 inguinal hernia, 1 diplopia, 1 staphylococcal sepsis, 1 animal bite, 1 hand fracture, 1 third nerve paralysis, 1 alcoholism, 1 dependence	8 out of 104
Pearlman 2014	Boceprevir	1 anaemia	1 out of 49	1 anaemia	1 out of 52
Poordad 2011a1	Boceprevir	7 anaemia, 1 atrial fibrillation, 1 coronary artery disease, 2 abdominal pain, 1 gastritis, 1 pancreatitis acute, 5 chest pain, 4 pyrexia, 1 cholecystitis, 4 pneumonia, 1 overdose, 1 dehydration, 1 back pain, 1 intervertebral disc protrusion, 5 syncope, 1 completed suicide, 2 depression, 4 suicidal ideation, 1 dyspnoea, 1 nausea, 2 vomiting, 3 neutropenia, 3 thrombocytopenia, 2 bronchitis, 3 cellulitis, 1 staphylococcal infection, 1 hyponatraemia, 1 pancytopenia, 1 breast cancer, 1 malaise, 1 pneumonia pneumococcal, 1 haemoptysis, 1 road traffic accident, 1 suicide attempt, 1 pruritus, 1 rash erythematous, 1 dizziness, 2 pulmonary embolism, 1 haemorrhoids, 4 gastroenteritis, 1 general physical health deterioration, 1 hypertensive crisis, 1 colon cancer, 1 drug abuse, 2 hypokalaemia, 2 chest discomfort, 1 fatigue, 1 perirectal abscess, 1 acute myocardial infarction, 1 gastrointestinal haemorrhage, 1 aplasia pure red cell, 2 leukopenia, 1 atrial flutter, 1 cardiac arrest, 1 hypertrophic cardiomyopathy, 1 tachycardia, 1 deafness, 1 conjunctivitis, 1 optic neuropathy, 1 papilledema, 1 abdominal pain lower, 1 colonic polyp, 1 gastroesophageal reflux disease, 1 hematemesis, 1 haemorrhoidal haemor-	87 out of 734	1 anaemia, 1 myocardial infarction, 1 abdominal pain, 2 pyrexia, 1 cholecystitis, 1 appendicitis, 1 pneumonia, 1 hepatic neoplasm malignant, 1 completed suicide, 1 depression, 1 suicidal ideation, 1 pneumothorax, 2 cholelithiasis, 1 nausea, 1 vomiting, 1 cellulitis, 1 breast cancer, 1 colitis, 1 upper respiratory tract infection, 1 suicide attempt, 2 death, 1 accidental overdose, 1 dizziness, 1 loss of consciousness, 1 cholecystitis acute, 1 sinusitis, 2 pancreatitis, 1	31 out of 363

Table 2. Serious adverse events *(Continued)*

		rhage, 1 Mallory-weiss syndrome, 1 umbilical hernia, 1 sarcoidosis, 1 abscess, 1 abscess limb, 1 bacteraemia, 1 epiglottitis, 1 infected bites, 1 injection site infection, 1 scrotal abscess, 1 tracheobronchitis, 1 post procedural complication, 1 transfusion reaction, 1 vascular pseudoaneurysm, 1 wound dehiscence, 1 flank pain, 1 groin pain, 1 musculoskeletal chest pain, 1 bladder cancer, 1 pancreatic carcinoma, 1 prostate cancer, 1 carotid artery stenosis, 1 cerebral ischaemia, 1 motor neurone disease, 1 muscle spasticity, 1 affective disorder, 1 alcohol abuse, 1 anxiety, 1 psychiatric decompensation, 1 scrotal pain, 2 cough, 1 pleural fibrosis, 1 alcohol use, 1 laryngeal operation, 1 accelerated hypertension, 1 arterial thrombosis limb, 2 hypotension		leukocytosis, 1 cardiac arrest, 1 cardio-respiratory arrest, 1 hypothyroidism, 1 cholelithiasis obstructive, 1 atypical mycobacterial infection, 1 diverticulitis, 1 enterocolitis infectious, 1 alcohol poisoning, 1 spinal fracture, 1 white blood cell count decreased, 1 lung adenocarcinoma, 1 prostate cancer, 1 hypoaesthesia, 1 affective disorder, 1 bipolar disorder, 1 drug dependence, 1 intentional self-injury, 1 personality disorder, 1 glomerulonephritis minimal lesion, 1 renal tubular necrosis, 1 physical assault, 1 cholecystectomy, 1 skin neoplasm excision	
Silva 2013a1	Boceprevir	None reported	0 out of 28	1 atrial fibrillation	1 out of 10
Sulkowski 2013a	Boceprevir	3 anaemia, 2 pneumonia, 1 syncope, 1 depression, 1 deep vein thrombosis, 1 lymphadenopathy, 1 renal failure acute, 2 pulmonary embolism, 1 arthralgia, 1 sinusitis, 1 urinary tract infection, 1 lung infection pseudomonal, 1 pelvic inflammatory disease, 1 pulmonary hypertension, 1 suicide attempt	11 out of 64	2 anaemia, 1 overdose, 1 cholelithiasis, 1 abdominal pain upper, 1 meniscus lesion, 1 pancreatitis, 1 post procedural infection, 1 renal failure, 1 cholecystectomy, 1 vulval abscess, 1 ventricular fibrillation, 1 ligament rupture, 1 lactic acidosis, 1 respiratory failure	7 out of 34
Dore 2015a1	Daclatasvir	1 hepatic neoplasm malignant, 1 rectal ulcer haemorrhage, 1 gastrointestinal in-	6 out of 196	1 abdominal pain upper, 1	3 out of 100

Table 2. Serious adverse events *(Continued)*

		flammation, 1 adhesion, 1 biliary colic, 1 hyperbilirubinaemia, 1 appendiceal abscess, 1 tonsil cancer		epicondylitis, 1 conversion disorder	
COMMAND-1 2015a1	Daclatasvir	1 anaemia, 1 abdominal pain, 1 gastritis, 1 chest pain, 2 pneumonia, 1 overdose, 1 syncope, 2 depression, 2 suicidal ideation, 1 dyspnoea, 1 bronchitis, 1 peritonitis, 1 rash generalised, 1 febrile neutropenia, 1 aplastic anaemia, 1 auricular perichondritis, 2 gastric ulcer haemorrhage, 1 death, 1 bile duct stone, 1 clostridium difficile, 1 furuncle, 1 carbuncle, 1 oral herpes, 1 accidental overdose, 2 falls, 1 bursitis, 1 rhabdomyolysis, 1 muscle spasms, 1 costochondritis, 1 dizziness, 1 loss of consciousness, 1 adjustment disorder, 1 hypomania, 1 mental disorder, 1 substance-induced psychotic disorder, 1 schizophrenia, paranoid type	25 out of 317	2 anaemia, 1 atrial fibrillation, 1 pneumonia, 1 pyelonephritis, 1 haemoglobin decreased, 1 epistaxis, 1 electrocardiogram change, 1 neutrophil count decreased, 1 myalgia, 1 aphasia, 1 paraesthesia	6 out of 78
Izumi 2014a1	Daclatasvir	1 pancreatitis acute, 1 back pain	2 out of 34	None reported	0 out of 8
Pol 2012	Daclatasvir	1 anaemia, 1 chest pain, 2 syncope, 1 bronchitis, 1 epistaxis	3 out of 36	None reported	0 out of 12
Dauphine 2015a1	Danoprevir	28 unspecified SAEs and 2 deaths	29 out of 373	1 unspecified SAE	1 out of 44
Forestier 2011a1	Danoprevir	1 benign paroxysmal vertigo	1 out of 40	None reported	0 out of 8
Forestier 2011b	Danoprevir	1 gastroenteritis viral	1 out of 47	None reported	0 out of 12
Gane 2011	Danoprevir	1 altered mood	1 out of 25	None reported	0 out of 5
ATLAS 2013	Danoprevir	14 SAEs but not specified, 1 death	15 out of 194	6 SAEs but not specified	6 out of 31
Larrey 2013	Deleobuvir	1 drug eruption	1 out of 46	None reported	0 out of 14
Larrey 2012	Deleobuvir	1 syncope, 1 rash maculo-papular, 1 umbilical hernia	3 out of 49	None reported	0 out of 8
STARTverso-2 2014a1	Faldaprevir	2 anaemia, 1 angina pectoris, 2 diarrhoea, 1 oesophageal varices haemorrhage, 1 cholecystitis, 2 pneumonia, 1 dehydration, 1 back pain, 1 intervertebral disc protrusion, 1 bipolar disorder, 1 depression, 1 suicidal ideation, 1 dyspnoea, 2 nausea, 3 vomiting, 2 neutropenia, 1 thrombocytopenia, 1 cellulitis, 1 mental status changes, 1 pancytopenia, 1 breast cancer, 1 malaise, 2 rash, 2 sepsis, 1 suicide attempt, 1 renal failure acute, 1 rash maculo-papular, 1 accidental overdose, 1 muscle spasm, 1 tibia fracture, 1 contusion, 1 pulmonary embolism, 2 abortion	47 out of 525	1 anaemia, 2 depression, 1 suicidal ideation, 1 bile duct stone, 1 subcutaneous abscess, 1 optic ischaemic neuropathy, 1 laceration, 1 mental status change	8 out of 132

Table 2. Serious adverse events *(Continued)*

		spontaneous, 1 hypokalaemia, 1 subcutaneous abscess, 1 acute myocardial infarction, 1 pancreatitis, 1 umbilical hernia, 1 diverticulitis, 1 cerebral ischaemia, 1 drug dependence, 1 personality disorder, 1 epidermolysis, 1 ascites, 1 duodenal ulcer haemorrhage, 1 large intestine perforation, 1 hepatic cirrhosis, 2 hepatic failure, 1 hypersensitivity, 1 infective chondritis, 1 vulval abscess, 1 fibula fracture, 1 jaw fracture, 1 ligament sprain, 1 hypocalcaemia, 1 hyponatraemia, 1 hepatocellular carcinoma, 1 papillary thyroid cancer			
STARTVerso-1 2015a1	Faldaprevir	3 anaemia, 1 atrial fibrillation, 1 myocardial infarction, 1 asthenia, 1 chest pain, 1 pyrexia, 1 bronchopneumonia, 1 pneumonia, 1 sciatica, 2 vomiting, 1 thrombocytopenia, 1 pancytopenia, 1 headache, 2 rash, 1 drug eruption, 1 dizziness, 1 haemorrhoids, 1 psychotic disorder, 1 urinary tract infection, 1 diabetes mellitus, 1 parapsoriasis, 1 pancreatitis, 1 histiocytosis haematophagic, 1 cerebrovascular accident, 1 muscular weakness, 1 epistaxis, 1 leukopenia, 1 sarcoidosis, 1 hypotension, 1 idiopathic thrombocytopenic purpura, 1 optic ischaemic neuropathy, 1 hypersensitivity, 1 hypoparathyroidism, 1 retinopathy, 1 subdural hematoma, 1 cervix carcinoma, 1 cubital tunnel syndrome, 1 dyspnoea exertional	34 out of 520	1 anaemia, 1 cholecystitis, 1 gun shot wound, 1 rash maculo-papular, 1 diverticulitis, 1 inguinal hernia, 1 hepatic lesion, 1 polymyositis, 1 blister	8 out of 132
STARTverso-3 2013a1	Faldaprevir	5 anaemia, 1 atrial fibrillation, 1 abdominal pain, 5 diarrhoea, 1 pancreatitis acute, 1 asthenia, 1 chest pain, 8 pyrexia, 2 appendicitis, 1 gastroenteritis viral, 2 pneumonia, 1 decreased appetite, 1 dehydration, 1 back pain, 1 hepatic neoplasm malignant, 2 cholelithiasis, 1 biliary colic, 2 hyperbilirubinaemia, 3 nausea, 2 vomiting, 1 thrombocytopenia, 1 cellulitis, 1 bradycardia, 2 presyncope, 2 malaise, 2 headache, 2 sepsis, 1 rash erythematous, 1 rash generalised, 1 fall, 1 multiple injuries, 1 haematochezia, 1 peritonitis bacterial, 1 congestive cardiac failure, 1 gastroenteritis, 1 hypertensive crisis, 1 hypokalaemia, 1 fatigue, 1 pancreatitis, 1 coma, 1 renal colic, 1 leukopenia, 1 cardio-respiratory arrest, 1 anxiety, 1 psychiatric decompensation, 2 hypotension, 1 viral infection, 2 ascites, 1 hepatic failure, 1 hypoglycaemia, 1 haemolytic anaemia, 1 keratosis follicular, 1 oral lichen planus, 1 peritoneal haemorrhage, 1 salivary gland calculus, 1 hepatorenal failure, 2 jaundice, 1 streptococcal infection, 1 blood lactate dehy-	54 out of 599	1 depression, 1 pleural effusion	1 out of 78

Table 2. Serious adverse events *(Continued)*

		drogenase increased, 1 international normalised ratio abnormal, 1 metabolic acidosis, 1 fasciitis, 1 joint instability, 1 musculoskeletal discomfort, 1 haemothorax, 1 venous thrombosis			
Nishiguchi 2014a1	Faldaprevir	1 abdominal pain upper	1 out of 35	1 abdominal pain	1 out of 8
Manns 2011	Faldaprevir	1 asthenia, 1 cataract , 1 hypoalbuminaemia, 1 metabolic disorder, 1 ascites	4 out of 88	None reported	0 out of 8
Sulkowski 2013a	Faldeprevir	4 anaemia, 1 angina pectoris, 1 myocardial infarction, 1 diarrhoea, 1 asthenia, 1 chest pain, 1 oedema peripheral, 4 pyrexia, 1 cholecystitis, 1 pneumonia, 2 dehydration, 1 intervertebral disc protrusion, 2 syncope, 1 depression, 1 nausea, 2 vomiting, 1 thrombocytopenia, 1 upper gastrointestinal haemorrhage, 1 influenza, 1 lower respiratory tract infection, 2 photosensitivity reaction, 1 upper respiratory tract infection, 2 headache, 1 rash, 1 road traffic accident, 2 suicide attempt, 3 drug eruption, 2 rash maculo-papular, 1 rash erythematous, 2 febrile neutropenia, 1 oral herpes, 1 pulmonary embolism, 1 pyelonephritis, 1 cataract, 1 anaemia haemolytic autoimmune, 1 lymphopenia, 1 microvascular angina, 1 prinzmetal angina, 1 anal fistula, 1 haemorrhoids, 1 mouth ulceration, 1 rectal haemorrhage, 1 chest discomfort, 1 fatigue, 1 mucosal inflammation, 1 gallbladder polyp, 1 cryoglobulinaemia, 1 anal abscess, 1 ear infection, 2 H1N1 influenza, 1 infected skin ulcer, 1 lymphangitis, 1 perirectal abscess, 1 pharyngitis, 1 subcutaneous abscess, 1 superinfection bacterial, 1 urinary tract infection, 1 diabetes mellitus, 1 ischaemic stroke, 1 acute psychosis, 1 depressed mood, 1 calculus ureteric, 1 endometrial hyperplasia, 1 dermatitis atopic, 1 eczema, 1 erythema multiforme, 1 lichen planus, 1 palmar-plantar erythrodysaesthesia syndrome, 1 parapsoriasis, 1 pruritus allergic, 1 rash pruritic, 1 appendicectomy	61 out of 641	1 headache, 1 photophobia, 1 cyst, 1 benign salivary gland neoplasm, 1 migraine	2 out of 71
Jacobson 2010	Filibuvir	1 blood creatinine increased, 1 chronic obstructive pulmonary disease, 1 pulmonary embolism	3 out of 27	1 thyroiditis, 1 gait disturbance	2 out of 8
Rodriguez-Torres 2014b1	Filibuvir	1 anaemia, 1 appendicitis, 1 rectal ulcer haemorrhage, 1 craniocerebral injury, 1 vertigo, 1 vestibular disorder, 1 haematochezia, 1 peritonitis bacterial, 1 lymph node tuberculosis, 1 scapula fracture, 1 blood urea nitrogen/creatinine increased, 1 gastric cancer, 1 rectal cancer, 1 abor-	20 out of 192	1 neutropenia, 1 sepsis, 1 pulmonary embolism, 1 cerebral haemorrhage, 1 ecchy-	6 out of 96

Table 2. Serious adverse events *(Continued)*

		tion spontaneous, 1 cardiac necrosis, 1 pyoderma gangrenosum, 1 depression, 1 breast cancer, 1 chronic obstructive pulmonary disease, 1 lung neoplasm malignant, 1 fall, 1 loss of consciousness, 1 bacterial abscess CNS, 1 actinomyces test positive, 1 pulmonary calcification		mosis, 1 Appendicitis perforated	
Lawitz 2013b	GS-9451	1 death, 1 heroin overdose	1 out of 33	None reported	0 out of 8
Gardner 2014a	GSK2336805	1 pneumonia, 1 upper lobe cavitary lesion	1 out of 11	None reported	0 out of 4
Lalezari 2013	IDX-184	1 pancreatitis, 1 acute cholecystitis	2 out of 65	1 agitation	1 out of 16
Gane 2010	Mericitabine/danoprevir	1 multiple drug overdose, 1 ankle fracture	2 out of 73	None reported	0 out of 14
Feld 2015	Mericitabine	1 nephrolithiasis, 1 porphyria non-acute	2 out of 102	1 arthritis infective	1 out of 49
JUMP-C 2013	Mericitabine	6 SAEs but not specified	5 out of 81	4 SAEs but not specified	3 out of 85
De Bruijne 2010a1	Narlaprevir	1 pyrexia, 1 elevated CRP	1 out of 32	None reported	0 out of 8
Muir 2014	Odalasvir (ACH-3102) and sovaprevir	1 non-cardiac chest pain	1 out of 20	None reported	0 out of 10
Zeuzem 2014a	Paritaprevir (ABT-450)/r–ombitasvir	1 pneumonia, 1 nausea, 1 vomiting, 1 bradycardia, 1 chronic obstructive pulmonary disease, 1 renal failure acute, 1 dizziness, 1 intestinal obstruction, 1 cerebrovascular accident, 1 bile duct stone, 1 calculus ureteric, 1 angioedema	9 out of 393	1 atrial fibrillation	1 out of 97
Anderson 2014a1	Paritaprevir/ABT-072/dasabuvir	1 haemorrhoids, 1 malignant melanoma	2 out of 63	None reported	0 out of 11
Feld 2014	Paritaprevir/ombitasvir	1 anaemia, 1 abdominal pain, 1 diarrhoea, 1 cholecystitis, 1 appendicitis, 1 overdose, 1 sinus tachycardia, 1 ventricular extrasystoles, 1 nausea, 1 vomiting, 1 chills, 1 non-cardiac chest pain, 1 lobar pneumonia, 1 postoperative wound infection, 1 lumbar vertebral fracture, 1 non-small cell lung cancer, 1 encephalopathy, 1 acute respiratory failure, 1 hypoxia, 1 mediastinal mass, 1 aortic stenosis, 1 biliary colic, 1 subcutaneous abscess	12 out of 630	None reported	0 out of 158
Pockros 2008a1	R1626	6 SAEs but not specified	6 out of 84	1 SAE but not specified	1 out of 20

Table 2. Serious adverse events *(Continued)*

Forns 2014	Simeprevir	1 abdominal pain, 1 pyrexia, 1 appendicitis, 2 pneumonia, 1 depression, 1 dyspnoea, 1 cholelithiasis, 1 anaemia haemolytic autoimmune, 1 pancytopenia, 1 angina pectoris, 1 bradycardia, 1 myocardial ischaemia, 1 hepatitis, 1 endocarditis, 1 lower respiratory tract infection, 1 septic shock, 1 breast cancer, 1 Guillain-Barre syndrome, 1 presyncope, 1 confusional state, 1 vaginal haemorrhage, 1 chronic obstructive pulmonary disease, 1 respiratory acidosis, 1 photosensitivity reaction	14 out of 260	1 atrial fibrillation, 1 depression, 1 bronchitis, 1 hypercalcaemia, 1 head injury, 1 bacterial prostatitis, 1 pericarditis, 1 infection, 1 inguinal hernia, 1 neuropathy peripheral, 1 arthritis infective, 1 headache	11 out of 133
Fried 2013	Simeprevir	1 cholecystitis, 1 intervertebral disc protrusion, 1 depression, 1 nausea, 1 breast cancer, 1 hyperthyroidism, 1 ocular vasculitis, 1 abdominal pain upper, 1 colitis, 1 small intestinal obstruction, 1 malaise, 1 incision site cellulitis, 1 necrotising fasciitis, 1 perihepatic abscess, 1 pneumonia pneumococcal, 1 upper respiratory tract infection, 1 post-procedural bile leak, 1 malnutrition, 1 type 1 diabetes mellitus, 1 spinal disorder, 1 parathyroid tumour benign, 1 headache, 1 haemoptysis, 1 cutaneous vasculitis, 1 hypertension	20 out of 309	1 myocardial infarction, 1 myopericarditis, 1 asthenia, 1 appendicitis, 1 vomiting, 1 chronic obstructive pulmonary disease, 1 headache, 1 subcutaneous abscess, 1 vulval abscess, 1 myositis, 1 ovarian neoplasm	10 out of 77
DRAGON 2014a1	Simeprevir	1 subarachnoid haemorrhage, 1 malaise, 1 cerebral infarction, 1 vulvar erosion, 1 rash, 1 incorrect dose administered	5 out of 79	None reported	0 out of 13
Hoeben 2015a1	Simeprevir	1 depression, 1 non-cardiac chest pain, 1 angina unstable, 1 nephrolithiasis, 1 ureteric stenosis, 1 colitis ischaemic, 1 incision site infection, 1 craniocerebral injury, 1 foot fracture, 1 meniscus lesion, 1 multiple injuries, 1 rib fracture, 1 tibia fracture, 1 traumatic lung injury, 1 wound, 1 cholesterosis, 1 type 2 diabetes mellitus, 1 shock haemorrhagic	10 out of 305	1 anaemia, 1 decreased appetite, 1 cholelithiasis, 1 contusion, 1 supraventricular tachycardia, 1 ligament sprain, 1 pain, 1 atypical pneumonia, 1 chronic hepatitis C, 1 pulmonary tuberculosis, 1 undifferentiated connective tissue disease, 1 brain neoplasm	9 out of 152
OPERA 2011a1	Simeprevir	1 sinus arrest, 1 erysipelas, 1 type 1 diabetes mellitus, 1 psychotic disorder, 1 drug abuse, 1 bronchitis, 1 exostosis, 1 toe deformity, 1 hyperthyroidism, 1 Bowen's disease, 1 neutropenia, 1 thrombocytopenia, 1 breast cancer, 1 sepsis, 1	13 out of 88	1 pneumonia, 1 sinusitis, 1 panic attack, 1 social stay hospitalisation, 1 pneumonia escherichia	3 out of 28

Table 2. Serious adverse events *(Continued)*

		cupulolithiasis, 1 pneumonia escherichia, 1 panic reaction			
Manns 2014a	Simeprevir	2 anaemia, 1 back pain, 1 syncope, 1 hyperthyroidism, 1 death, 1 muscle spasms, 1 colon cancer, 1 anal abscess, 1 urinary tract infection, 1 mixed deafness, 1 hyphaema, 1 visual impairment, 1 enterocutaneous fistula, 1 autoimmune hepatitis, 1 lymphadenitis bacteria, 1 fluid overload, 1 epilepsy, 1 memory impairment, 1 aggression	16 out of 257	1 anaemia, 1 pancreatitis acute, 1 dehydration, 1 vomiting, 1 pancytopenia, 1 loss of consciousness, 1 angina unstable, 1 meniscus lesion, 1 pulmonary embolism, 1 cholecystitis acute, 1 drug abuse, 1 retinal ischaemia, 1 respiratory tract infection viral, 1 viral infection, 1 neuropathy peripheral, 1 thoracic outlet syndrome	10 out of 134
Pearlman 2015	Simeprevir	None reported	0 out of 58	1 liver decompensation	1 out of 24
ASPIRE 2014	Simeprevir	1 anaemia, 1 abdominal pain, 1 diarrhoea, 1 oedema peripheral, 2 cholecystitis, 1 pneumonia, 1 overdose, 2 dehydration, 1 intervertebral disc protrusion, 1 hepatic neoplasm malignant, 2 vomiting, 1 non-cardiac chest pain, 1 neutropenia, 2 cellulitis, 1 pancytopenia, 1 headache, 1 hypertension, 1 suicide attempt, 1 drug eruption, 2 clostridium difficile colitis, 1 nephrolithiasis, 1 pulmonary embolism, 1 rectal cancer, 1 sinusitis, 3 urinary tract infection, 1 diabetes mellitus, 1 migraine, 1 coma, 1 epistaxis, 1 alcohol abuse, 1 haemorrhagic anaemia, 1 cervix carcinoma, 1 periodontal disease, 1 enteritis, 1 gastro intestinal pain, 1 gingival infection, 1 lung infection, 1 meningitis bacterial, 1 pneumonia bordetella, 1 salpingitis, 1 thermal burn, 1 neurilemmoma benign, 1 brain injury, 1 cerebral haemorrhage, 1 vii nerve paralysis, 1 metrorrhagia, 1 pelvic adhesions	31 out of 396	1 sciatica, 1 nausea, 1 vomiting, 1 lower respiratory tract infection, 1 haemorrhoids, 1 weight decreased, 1 histiocytosis haematophagic, 1 tuberculosis	4 out of 66
POSITRON 2013	Sofosbuvir	1 drug withdrawal syndrome, 1 non-cardiac chest pain, 1 oedema peripheral, 1 pyrexia, 1 hypersensitivity, 1 abdominal abscess, 1 cellulitis, 2 overdose, 1 injury, 1 road traffic accident, 1 spinal compression fracture, 1 hypoglycaemia, 1 hepatic	11 out of 207	1 pancreatitis, 1 bile duct stone, 1 bronchitis	2 out of 71

Table 2. Serious adverse events *(Continued)*

		neoplasm malignant, 1 abnormal behaviour, 1 eczema			
Lawitz 2013a1	Sofosbuvir	1 retinal vein occlusion, 1 depression, 1 suicidal ideation, 1 lymphangitis, 1 acute myocardial infarction	4 out of 95	1 chest pain, 1 electrocardiogram ST segment elevation	1 out of 26
FISSION 2013	Sofosbuvir	1 anaemia, 1 chest pain, 1 cellulitis, 1 chronic obstructive pulmonary disease, 1 urinary tract infection, 1 allergy to anthropod sting, 1 osteomyelitis chronic , 1 toxicity to various agents	7 out of 256	1 pneumothorax, 1 breast cancer, 1 infection, 1 atrioventricular shock, 1 clavicle fracture, 1 rib fracture	3 out of 243
Rodriguez-Torres 2013	Sofosbuvir	1 anaemia, 1 depression, 1 peripheral ischaemia, 1 pancreatitis acute	4 out of 49	1 abdominal pain	1 out of 14
Feld 2015	Sofosbuvir/velpatasvir	1 bronchitis, 1 cellulitis, 1 influenza, 1 chronic obstructive pulmonary disease, 1 death, 1 gastroenteritis, 1 acute myocardial infarct, 1 ligament sprain, 1 foot abscess, 1 foot necrosis, 1 recurring appendicitis, 1 epileptic seizure, 1 rotator cuff syndrome, 1 lung cancer, 1 mania, 1 palpitations, 1 small bowel obstruction, 1 upper limb fracture, 1 vestibular neuronitis	15 out of 624	None reported	0 out of 116
Benhamou 2013a1	Telaprevir	1 cholelithiasis	1 out of 16	None reported	0 out of 8
Hezode 2009	Telaprevir	5 anaemia, 2 abdominal pain, 1 asthenia, 1 pyrexia, 1 back pain, 3 syncope, 3 depression, 2 dyspnoea, 1 nausea, 1 chills, 1 pancytopenia, 5 rash, 1 lymphadenopathy, 1 hydrocele, 1 retinal haemorrhage, 1 catheter-related complication, 1 bacterial sepsis, 1 pneumonia, 1 herpes viral, 1 sepsis, 1 road traffic accident, 1 tendon rupture, 1 lung neoplasm malignant, 1 speech disorder, 1 disorientation, 1 emotional distress, 1 suicide attempt, 1 renal failure, 1 acute testicular swelling, 3 pruritis, 2 drug eruption, 2 rash maculo-papular, 1 rash erythematous, 1 rash generalised, 1 toxic skin eruption, 1 urticaria, 1 splenectomy	36 out of 241	2 anaemia, 1 angina pectoris, 1 syncope, 1 hyperthyroidism, 1 gastroenteritis, 1 haemorrhagic anaemia, 1 alcoholic pancreatitis, 1 paranoia, 1 uterine polyp	8 out of 82
ADVANCE 2011a1	Telaprevir	18 anaemia, 3 pneumonia, 3 syncope, 2 cellulitis, 5 rash, 3 psychiatric disorder, 2 musculoskeletal disorder, 2 cardiac disorder, 2 eye disorder, 3 hepatobiliary disorders, 2 vascular disorder	64 out of 727	4 anaemia, 1 cellulitis, 3 psychiatric disorder, 3 musculoskeletal disorder, 2 cardiac disorder, 4 renal and urinary disorder, 1 eye	24 out of 361

Table 2. Serious adverse events *(Continued)*

				disorder, 1 vascular disorder	
McHutchison 2009	Telaprevir	2 anaemia, 1 gastroenteritis viral, 1 dehydration, 2 depression, 1 non-cardiac chest pain, 1 chronic obstructive pulmonary disease, 1 rash, 1 rash generalised, 1 furuncle, 1 colitis ischaemic, 1 acute myocardial infarction, 1 adrenal disorder, 2 scotoma, 1 retinal exudates, 1 retinal infarction, 1 bronchitis bacterial, 1 incisional hernia, 1 lumbar radiculopathy, 1 exfoliative rash	18 out of 175	1 lobar pneumonia, 1 pancytopenia, 1 anxiety, 1 lymphadenitis bacteria, 1 deafness neurosensory	4 out of 75
McHutchison 2010	Telaprevir	6 anaemia, 1 pancreatitis acute, 1 gastroenteritis viral, 1 pneumonia, 1 dehydration, 1 back pain, 1 suicidal ideation, 2 cholelithiasis, 1 postoperative wound infection, 1 upper gastrointestinal haemorrhage, 1 confusional state, 2 small intestinal obstruction, 1 necrotising fasciitis, 1 pneumonia pneumococcal, 1 postprocedural bile leak, 1 rash, 1 renal failure acute, 1 retinal detachment, 9 gastroenteritis, 1 cholecystitis acute, 1 sinusitis, 1 hypokalaemia, 1 eczema, 2 pancreatitis, 1 dermatitis, 1 diverticulitis, 1 alcohol abuse, 1 hypotension, 1 haemorrhagic anaemia, 1 idiopathic thrombocytopenic purpura, 1 cardiomyopathy, 1 diverticular perforation, 1 gastritis erosive, 1 abscess intestinal, 1 cholecystitis infective, 1 infected insect bite, 1 sepsis syndrome, 1 hypovolaemia, 1 B-cell unclassifiable lymphoma low grade, 1 migraine with aura, 1 ruptured cerebral aneurysm, 1 neurogenic bladder, 1 lichenoid keratosis, 1 rash macular	28 out of 339	1 anaemia, 1 pneumonia, 2 dehydration, 1 syncope, 1 depression, 1 non-small cell lung cancer, 1 headache, 2 rash, 1 renal failure acute, 2 gastroenteritis, 1 renal tubular acidosis, 1 decubitus ulcer, 1 hematoma	9 out of 114
Sulkowski 2013a	Telaprevir	1 myocardial infarction, 1 staphylococcal infection, 1 pyelonephritis acute, 1 haemolytic anaemia, 1 groin infection, 1 cellulitis staphylococcal, 1 staphylococcal abscess, 1 hypokalaemia, 1 hyponatraemia, 1 epididymitis, 1 non- cardiac chest pain	7 out of 38	1 anaemia, 1 appendicitis, 1 peritonitis	2 out of 22
Zeuzem 2011a	Telaprevir	13 anaemia, 1 febrile neutropenia, 2 pancytopenia, 1 thrombocytopenia , 3 acute myocardial infarction, 2 atrial fibrillation, 1 cardiac valve disease, 1 myocardial infarction, 1 supraventricular tachycardia, 1 sudden hearing loss, 1 Basedow's disease, 1 retinal detachment, 1 abdominal pain, 1 anal fissure, 1 caecitis, 1 gastrointestinal haemorrhage, 1 pancreatitis, 2 pancreatitis acute, 1 general physical health deterioration, 1 pyrexia, 1 appendicitis, 2 bronchitis, 1 erysipelas, 1 folliculitis, 1 Helicobacter gastritis, 1 pneu-	65 out of 530	1 anaemia, 1 atrial fibrillation, 1 abdominal pain, 1 pneumonia, 1 colitis, 1 pyelonephritis, 1 cerebral thrombosis, 1 coma	7 out of 132

Table 2. Serious adverse events *(Continued)*

		monia, 1 post-procedural infection, 1 rectal abscess, 2 sepsis, 1 sinusitis, 1 tooth abscess, 2 urinary tract infection, 1 injection site reaction, 1 animal scratch, 1 ankle fracture, 1 femoral neck fracture, 1 multiple drug overdose, 1 blood corticotrophin decreased, 1 weight decreased, 1 anorexia, 1 diabetes mellitus, 1 bronchial carcinoma, 2 gastric cancer, 2 hepatic neoplasm malignant, 1 histiocytosis haematophagic, 1 lung neoplasm malignant, 1 lethargy, 1 subarachnoid haemorrhage, 2 syncope, 1 delirium, 1 depression, 1 insomnia, 1 substance abuse, 1 renal cyst, 1 renal failure, 1 urinary bladder polyp, 1 prostatitis, 1 pulmonary embolism, 1 dermatitis, 1 eczema , 1 erythema multiforme, 1 pruritus 1 pustular psoriasis, 1 rash, 2 toxic skin eruption, 1 orthostatic hypotension, 1 peripheral artery aneurysm			
Manns 2012a1	Vaniprevir	1 appendicitis, 1 lobar pneumonia, 1 septic shock, 1 confusional state, 1 gastroenteritis, 1 cholecystitis acute, 1 empyema, 1 haemoglobin decreased, 1 myopathy	8 out of 75	1 colon cancer	1 out of 19
Lawitz 2013c	Vaniprevir	1 anaemia, 1 pneumonia, 1 syncope, 1 upper gastrointestinal haemorrhage, 1 cellulitis, 1 confusional state, 1 dizziness, 1 nephrolithiasis, 1 malignant melanoma, 3 retinal detachment, 1 joint dislocation, 1 congestive cardiac failure, 2 gastroenteritis, 1 femur fracture, 1 hyperglycaemia, 1 dermatomyositis, 1 retinal vascular thrombosis, 1 general physical health deterioration, 1 anaphylactic reaction, 1 pyelonephritis, 1 pyelonephritis acute, 1 carbon monoxide poisoning, 1 arthralgia, 1 arthritis infective, 1 completed suicide	22 out of 229	1 hypertensive crisis	1 out of 56

SAE: serious adverse events.

Table 3. Non-serious adverse events

Trial	Experimental intervention	Type and number of participants with a non-serious adverse events (experimental group)	Proportion of participants with a non-serious adverse event (experimental group)	Type and number of participants with a non-serious adverse events (control group)	Proportion of participants with a non-serious adverse event (control group)
Bronowicki 2013a1	Asunaprevir	18 diarrhoea, 13 nausea, 10 asthenia, 21 fatigue, 14 influenza-like illness, 7 irritability, 12 decreased appetite, 4 arthralgia, 9 myalgia, 13 headache,	36 out of 36	1 diarrhoea, 2 nausea, 4 asthenia, 5 fatigue, 5 influenza-like illness, 4 irritability, 3 decreased appetite, 4 arthralgia, 1 myalgia, 6	11 out of 11

Table 3. Non-serious adverse events *(Continued)*

		9 depression, 10 insomnia, 7 cough, 10 dyspnoea, 7 alopecia, 11 dry skin, 10 pruritus, 6 rash		headache, 1 depression, 1 insomnia, 3 cough, 3 dyspnoea, 3 alopecia, 1 dry skin, 2 pruritus, 3 rash	
Bronowicki 2014	Asunaprevir	8 anaemia, 63 asthenia, 62 fatigue, 37 influenza-like illness, 43 decreased appetite, 66 headache, 41 pruritus	173 out of 177	3 anaemia, 1 asthenia, 62 fatigue, 23 influenza-like illness, 22 decreased appetite, 26 headache, 16 pruritus	57 out of 61
Pasquinelli 2012a1	Asunaprevir	1 nausea, 3 headache, 1 flatulence	Not specified out of 20	None reported	Not specified out of 4
Pasquinelli 2012a2	Asunaprevir	1 nausea, 3 headache	Not specified out of 12	1 nausea, 1 flatulence	Not specified out of 3
Nelson 2012a1	Balapiravir	120 anaemia, 41 neutropenia, 115 diarrhoea, 162 nausea, 138 chills, 231 fatigue, 117 pyrexia, 100 arthralgia, 156 myalgia, 82 dizziness, 241 headache, 90 depression, 174 insomnia, 86 cough, 88 alopecia, 60 dry skin, 108 pruritus, 90 rash	Not specified out of 432	6 anaemia, 3 neutropenia, 16 diarrhoea, 25 nausea, 30 chills, 43 fatigue, 19 pyrexia, 16 arthralgia, 33 myalgia, 15 dizziness, 42 headache, 17 depression, 24 insomnia, 11 cough, 11 alopecia, 16 dry skin, 15 pruritus, 13 rash	Not specified out of 72
Tatum 2015a1	Beclabuvir	5 anaemia, 5 neutropenia, 5 diarrhoea, 9 nausea, 3 chills, 12 fatigue, 6 influenza-like illness, 7 irritability, 3 pyrexia, 7 decreased appetite, 4 arthralgia, 5 myalgia, 12 headache, 6 depression, 9 insomnia, 6 cough, 5 pruritus, 2 rash	Not specified out of 26	5 anaemia, 1 neutropenia, 1 diarrhoea, 2 nausea, 5 fatigue, 7 influenza-like illness, 3 irritability, 1 pyrexia, 2 decreased appetite, 3 headache, 3 depression, 3 insomnia, 3 cough, 4 pruritus, 4 rash	Not specified out of 13
Erhardt 2009	BILB-1941	25 diarrhoea, 7 nausea, 2 vomiting	30 out of 77	2 diarrhoea	3 out of 19
Sims 2014	BMS-791325	1 diarrhoea, 1 nausea, 1 vomiting, 1 headache, 1 pruritus	9 out of 20	1 nausea, 1 vomiting, 1 headache	1 out of 4
Bacon 2011a1	Boceprevir	145 anaemia, 46 neutropenia, 78 diarrhoea, 140 nausea, 47 vomiting, 68 asthenia, 106 chills, 179 fatigue, 79 influenza-like illness, 67 irritability, 93 pyrexia, 83 decreased appetite, 73 arthralgia, 81 myalgia, 52 dizziness, 142 dysgeusia, 133 headache, 46 depression, 97 insomnia, 70 cough, 69 dyspnoea, 71 alopecia, 72 dry skin, 62 pruritus, 51 rash	319 out of 323	16 anaemia, 8 neutropenia, 13 diarrhoea, 30 nausea, 6 vomiting, 13 asthenia, 24 chills, 40 fatigue, 20 influenza-like illness, 10 irritability, 20 pyrexia, 13 decreased appetite, 13 arthralgia, 19 myalgia, 8 dizziness, 9 dysgeusia, 39 headache, 12 depression, 19 insomnia, 14 cough, 14 dyspnoea, 13 alopecia, 7 dry skin, 14 pruritus, 5 rash	77 out of 80
Flamm 2013	Boceprevir	67 anaemia, 41 neutropenia, 33 diarrhoea, 52 nausea, 16 vomiting, 29 asthenia, 14 chills, 67 fatigue, 35 influen-	133 out of 134	22 anaemia, 12 neutropenia, 5 diarrhoea, 18 nausea, 12 asthenia, 8 chills, 36 fatigue, 18 influenza-like ill-	67 out of 67

Table 3. Non-serious adverse events *(Continued)*

		za-like illness, 29 irritability, 18 pyrexia, 27 decreased appetite, 16 arthralgia, 25 myalgia, 17 dizziness, 52 dysgeusia, 37 headache, 22 depression, 32 insomnia, 26 cough, 26 dyspnoea, 22 alopecia, 20 dry skin, 18 pruritus, 31 rash		ness, 16 irritability, 8 pyrexia, 12 decreased appetite, 12 arthralgia, 5 myalgia, 10 dizziness, 10 dysgeusia, 21 headache, 6 depression, 20 insomnia, 14 cough, 17 dyspnoea, 5 alopecia, 11 dry skin, 8 pruritus, 5 rash	
Isakov 2016	Boceprevir	105 anaemia, 103 leukopenia, 141 neutropenia, 16 thrombocytopenia, 22 diarrhoea, 13 dry mouth, 59 nausea, 12 vomiting, 63 asthenia, 24 chills, 40 fatigue, 51 hyperthermia, 356 influenza-like illness, 9 injection site erythema, 18 irritability, 217 pyrexia, 14 body temperature increased, 33 weight decreased, 10 decreased appetite, 16 arthralgia, 33 myalgia, 9 dizziness, 69 dysgeusia, 89 headache, 2 sleep disorder, 38 cough, 7 dyspnoea, 33 alopecia, 12 dry skin, 20 pruritus, 17 rash	153 out of 159	31 anaemia, 35 leukopenia, 45 neutropenia, 7 thrombocytopenia, 3 diarrhoea, 5 dry mouth, 15 nausea, 2 vomiting, 23 asthenia, 2 chills, 18 fatigue, 12 hyperthermia, 72 influenza-like illness, 2 injection site erythema, 11 irritability, 124 pyrexia, 2 body temperature increased, 9 weight decreased, 7 decreased appetite, 4 arthralgia, 8 myalgia, 7 dizziness, 5 dysgeusia, 51 headache, 4 sleep disorder, 14 cough, 7 dyspnoea, 16 alopecia, 3 dry skin, 6 pruritus, 2 rash	71 out of 78
Kwo 2010a1	Boceprevir	226 anaemia, 96 neutropenia, 109 diarrhoea, 186 nausea, 81 vomiting, 53 asthenia, 130 chills, 259 fatigue, 79 influenza-like illness, 91 irritability, 129 pyrexia, 49 decreased appetite, 76 arthralgia, 99 myalgia, 70 dizziness, 111 dysgeusia, 190 headache, 91 depression, 146 insomnia, 76 cough, 66 dyspnoea, 131 alopecia, 60 dry skin, 80 pruritus, 27 rash	413 out of 416	35 anaemia, 12 neutropenia, 23 diarrhoea, 45 nausea, 5 vomiting, 14 asthenia, 35 chills, 57 fatigue, 25 influenza-like illness, 23 irritability, 35 pyrexia, 12 decreased appetite, 21 arthralgia, 17 myalgia, 16 dizziness, 9 dysgeusia, 45 headache, 22 depression, 40 insomnia, 20 cough, 15 dyspnoea, 27 alopecia, 17 dry skin, 16 pruritus, 6 rash	102 out of 104
Poordad 2011a1	Boceprevir	361 anaemia, 184 neutropenia, 180 diarrhoea, 334 nausea, 145 vomiting, 125 asthenia, 255 chills, 405 fatigue, 174 influenza-like illness, 164 irritability, 240 pyrexia, 186 decreased appetite, 141 arthralgia, 170 myalgia, 146 dizziness, 293 dysgeusia, 335 headache, 151 depression, 239 insomnia, 130 cough, 152 dyspnoea, 179 alopecia, 153 dry skin, 181 pruritus, 181 rash	728 out of 734	107 anaemia, 77 neutropenia, 79 diarrhoea, 153 nausea, 57 vomiting, 70 asthenia, 102 chills, 217 fatigue, 93 influenza-like illness, 86 irritability, 120 pyrexia, 90 decreased appetite, 66 arthralgia, 94 myalgia, 59 dizziness, 64 dysgeusia, 153 headache, 78 depression, 118 insomnia, 76 cough, 59 dyspnoea, 99 alopecia, 66 dry skin, 98 pruritus, 83 rash	353 out of 363

Table 3. Non-serious adverse events *(Continued)*

Sulkowski 2013a	Boceprevir	26 anaemia, 12 neutropenia, 21 diarrhoea, 26 nausea, 18 vomiting, 22 asthenia, 5 chills, 25 fatigue, 16 influenza-like illness, 10 irritability, 24 pyrexia, 22 decreased appetite, 7 arthralgia, 9 myalgia, 8 dizziness, 18 dysgeusia, 18 headache, 11 depression, 15 insomnia, 9 cough, 5 dyspnoea, 12 alopecia, 8 dry skin, 13 pruritus, 5 rash	62 out of 64	8 anaemia, 2 neutropenia, 6 diarrhoea, 11 nausea, 5 vomiting, 9 asthenia, 5 chills, 12 fatigue, 13 influenza-like illness, 5 irritability, 7 pyrexia, 6 decreased appetite, 2 arthralgia, 6 myalgia, 2 dizziness, 5 dysgeusia, 6 headache, 4 depression, 9 insomnia, 6 cough, 2 dyspnoea, 6 alopecia, 3 dry skin, 3 pruritus	33 out of 34
Dore 2015a1	Daclatasvir	7 anaemia, 9 neutropenia, 10 diarrhoea, 22 nausea, 4 vomiting, 13 asthenia, 4 chills, 35 fatigue, 19 influenza-like illness, 17 irritability, 7 pyrexia, 12 decreased appetite, 11 arthralgia, 14 myalgia, 6 dizziness, 5 dysgeusia, 30 headache, 11 depression, 19 insomnia, 8 cough, 12 dyspnoea, 12 alopecia, 13 dry skin, 27 pruritus, 25 rash	98 out of 100	5 anaemia, 8 neutropenia, 3 diarrhoea, 8 nausea, 4 vomiting, 7 asthenia, 19 fatigue, 7 influenza-like illness, 6 irritability, 2 pyrexia, 8 decreased appetite, 9 arthralgia, 11 myalgia, 6 dizziness, 3 dysgeusia, 9 headache, 9 depression, 17 insomnia, 8 cough, 6 dyspnoea, 5 alopecia, 6 dry skin, 14 pruritus, 12 rash	48 out of 51
COMMAND-1 2015a1	Daclatasvir	53 anaemia, 43 neutropenia, 73 diarrhoea, 109 nausea, 34 vomiting, 32 asthenia, 49 chills, 174 fatigue, 94 influenza-like illness, 72 irritability, 48 pyrexia, 67 decreased appetite, 55 arthralgia, 88 myalgia, 46 dizziness, 25 dysgeusia, 136 headache, 45 depression, 102 insomnia, 54 cough, 58 dyspnoea, 80 alopecia, 88 dry skin, 119 pruritus, 94 rash	311 out of 317	9 anaemia, 9 neutropenia, 14 diarrhoea, 20 nausea, 11 vomiting, 7 asthenia, 16 chills, 46 fatigue, 16 influenza-like illness, 22 irritability, 15 pyrexia, 17 decreased appetite, 19 arthralgia, 24 myalgia, 9 dizziness, 4 dysgeusia, 36 headache, 10 depression, 30 insomnia, 18 cough, 11 dyspnoea, 13 alopecia, 15 dry skin, 26 pruritus, 25 rash	76 out of 78
Izumi 2014a1	Daclatasvir	11 anaemia, 7 neutropenia, 2 diarrhoea, 4 nausea, 6 fatigue, 1 irritability, 11 pyrexia, 7 decreased appetite, 4 arthralgia, 1 myalgia, 1 dizziness, 4 dysgeusia, 3 headache, 7 insomnia, 4 cough, 2 dyspnoea, 8 alopecia, 1 dry skin, 6 pruritus, 7 rash	34 out of 34	5 anaemia, 4 neutropenia, 3 diarrhoea, 2 nausea, 3 vomiting, 4 chills, 4 fatigue, 2 influenza-like illness, 5 pyrexia, 5 decreased appetite, 2 arthralgia, 2 myalgia, 1 dizziness, 1 dysgeusia, 4 headache, 2 insomnia, 1 cough, 6 alopecia, 1 dry skin, 3 pruritus, 3 rash	8 out of 8
Pol 2012	Daclatasvir	14 anaemia, 9 neutropenia, 5 diarrhoea, 13 nausea, 7 vomiting, 9 asthenia, 4 chills, 19 fatigue, 11 influenza-like illness, 12 irritability, 7 pyrexia, 9 decreased appetite, 2 arthralgia, 8 myalgia, 5 dizziness, 2 dysgeusia, 19 headache, 7 depression, 9 insomnia, 9 cough, 6	36 out of 36	5 anaemia, 5 neutropenia, 3 diarrhoea, 6 nausea, 1 asthenia, 2 chills, 9 fatigue, 4 influenza-like illness, 2 irritability, 3 pyrexia, 3 decreased appetite, 3 myalgia, 1 dizziness, 1 dysgeusia, 3 headache, 3 depression, 6 insomnia, 3 cough, 2 dysp-	12 out of 12

Table 3. Non-serious adverse events *(Continued)*

		dyspnoea, 8 alopecia, 2 dry skin, 12 pruritus, 10 rash		noea, 2 alopecia, 1 dry skin, 3 pruritus, 3 rash	
Nettles 2010	Daclatasvir	1 diarrhoea, 1 nausea, 4 headache	7 out of 16	None reported	0 out of 2
Nettles 2011a1	Daclatasvir	2 diarrhoea, 3 fatigue, 1 arthralgia, 1 dizziness, 5 headache, 2 insomnia, 1 dry skin	16 out of 24	1 nausea, 1 vomiting, 2 headache	4 out of 6
Dauphine 2015a1	Danoprevir	115 diarrhoea, 106 nausea, 77 asthenia, 89 chills, 158 fatigue, 125 pyrexia, 88 decreased appetite, 72 arthralgia, 93 myalgia,158 headache, 102 insomnia, 62 cough, 54 alopecia, 83 pruritus, 78 rash	364 out of 373	5 diarrhoea, 13 nausea, 9 asthenia, 8 chills, 17 fatigue, 15 pyrexia, 6 decreased appetite, 9 arthralgia, 13 myalgia, 24 headache, 16 insomnia, 12 cough, 4 alopecia, 14 pruritus, 6 rash	42 out of 44
Forestier 2011a1	Danoprevir	2 diarrhoea, 3 myalgia, 5 headache	21 out of 40	1 diarrhoea, 2 headache	3 out of 10
Forestier 2011b	Danoprevir	6 neutropenia, 5 diarrhoea, 4 nausea, 3 asthenia, 5 chills, 8 fatigue, 4 influenza-like illness, 2 pyrexia, 2 arthralgia, 17 myalgia, 6 dizziness, 23 headache, 2 depression, 6 insomnia, 3 pruritus	42 out of 47	2 neutropenia, 2 diarrhoea, 1 nausea, 1 chills, 3 fatigue, 1 influenza-like illness, 1 arthralgia, 5 myalgia, 1 dizziness, 4 headache, 1 depression, 2 insomnia	12 out of 12
Gane 2011	Danoprevir	4 diarrhoea, 5 nausea, 5 fatigue, 3 influenza-like illness, 5 irritability, 5 arthralgia, 5 myalgia, 11 headache, 4 insomnia, 6 rash	24 out of 25	1 diarrhoea, 3 nausea, 1 fatigue, 2 myalgia, 4 headache, 2 insomnia	5 out of 5
Marcellin 2013a	Danoprevir	53 anaemia, 70 neutropenia, 56 diarrhoea, 85 nausea, 29 vomiting, 57 chills, 109 fatigue, 38 irritability, 51 pyrexia, 34 decreased appetite, 29 arthralgia, 60 myalgia, 92 headache, 42 depression, 69 insomnia, 31 alopecia, 46 pruritus, 42 rash	Not specified out of 194	13 anaemia, 11 neutropenia, 7 diarrhoea, 10 nausea, 4 vomiting, 13 chills, 14 fatigue, 7 irritability, 5 pyrexia, 4 decreased appetite, 9 arthralgia, 11 myalgia, 18 headache, 4 depression, 9 insomnia, 5 alopecia, 6 pruritus, 8 rash	Not specified out of 31
Larrey 2012	Deleobuvir	1 anaemia, 19 diarrhoea, 19 nausea, 11 vomiting, 16 asthenia, 3 chills, 12 fatigue, 14 influenza-like illness, 7 irritability, 6 pyrexia, 14 decreased appetite, 4 arthralgia, 4 myalgia, 6 dizziness, 4 dysgeusia, 20 headache, 15 insomnia, 6 cough, 3 dyspnoea, 1 alopecia, 6 dry skin, 5 pruritus, 8 rash	49 out of 49	1 nausea, 1 asthenia, 1 chills, 2 fatigue, 1 influenza-like illness, 2 irritability, 1 decreased appetite, 2 headache, 1 dry skin, 1 pruritus, 2 rash	7 out of 8
STARTverso-2 2014a1	Faldaprevir	114 anaemia, 59 neutropenia, 160 diarrhoea, 249 nausea,	513 out of 525	27 anaemia, 14 neutropenia, 23 diarrhoea, 52 nau-	130 out of 132

Table 3. Non-serious adverse events *(Continued)*

		110 vomiting, 29 asthenia, 78 chills, 246 fatigue, 39 influenza-like illness, 67 irritability, 79 pyrexia, 117 decreased appetite, 72 arthralgia, 100 myalgia, 80 dizziness, 31 dysgeusia, 165 headache, 68 depression, 137 insomnia, 89 cough, 53 dyspnoea, 96 alopecia, 67 dry skin, 164 pruritus, 298 rash		sea, 11 vomiting, 6 asthenia, 25 chills, 70 fatigue, 15 influenza-like illness, 27 irritability, 20 pyrexia, 26 decreased appetite, 22 arthralgia, 37 myalgia, 25 dizziness, 3 dysgeusia, 45 headache, 11 depression, 38 insomnia, 21 cough, 20 dyspnoea, 22 alopecia, 15 dry skin, 37 pruritus, 41 rash	
STARTVerso-1 2015a1	Faldaprevir	89 anaemia, 57 neutropenia, 121 diarrhoea, 168 nausea, 79 vomiting, 96 asthenia, 143 fatigue, 92 influenza-like illness, 37 irritability, 110 pyrexia, 87 decreased appetite, 39 arthralgia, 41 myalgia, 38 dizziness, 23 dysgeusia, 146 headache, 32 depression, 70 insomnia, 58 cough, 36 dyspnoea, 49 alopecia, 80 dry skin, 160 pruritus, 139 rash	496 out of 520	26 anaemia, 18 neutropenia, 17 diarrhoea, 19 nausea, 6 vomiting, 27 asthenia, 35 fatigue, 21 influenza-like illness, 9 irritability, 32 pyrexia, 22 decreased appetite, 14 arthralgia, 20 myalgia, 13 dizziness, 5 dysgeusia, 40 headache, 8 depression, 22 insomnia, 20 cough, 16 dyspnoea, 15 alopecia, 17 dry skin, 41 pruritus, 25 rash	120 out of 132
STARTverso-3 2013a1	Faldaprevir	98 anaemia, 65 neutropenia, 190 diarrhoea, 318 nausea, 171 vomiting, 108 asthenia, 32 chills, 204 fatigue, 107 influenza-like illness, 49 irritability, 113 pyrexia, 128 decreased appetite, 60 arthralgia, 72 myalgia, 37 dizziness, 39 dysgeusia, 182 headache, 52 depression, 118 insomnia, 99 cough, 47 dyspnoea, 53 alopecia, 108 dry skin, 225 pruritus, 160 rash	585 out of 599	8 anaemia, 12 neutropenia, 10 diarrhoea, 18 nausea, 5 vomiting, 21 asthenia, 5 chills, 16 fatigue, 15 influenza-like illness, 11 irritability, 14 pyrexia, 10 decreased appetite, 7 arthralgia, 8 myalgia, 6 dizziness, 4 dysgeusia, 22 headache, 10 depression, 13 insomnia, 16 cough, 7 dyspnoea, 4 alopecia, 12 dry skin, 23 pruritus, 16 rash	74 out of 78
Manns 2011	Faldaprevir	2 anaemia, 1 neutropenia, 4 diarrhoea, 7 nausea, 10 asthenia, 2 chills, 2 fatigue, 4 influenza-like illness, 4 irritability, 2 pyrexia, 1 decreased appetite, 7 myalgia, 1 dizziness, 6 headache, 2 depression, 5 insomnia, 2 cough, 1 alopecia, 5 dry skin, 3 pruritis, 1 rash	32 out of 26	1 diarrhoea, 2 nausea, 2 asthenia, 2 headache, 1 depression, 1 insomnia, 1 cough	5 out of 8
Nishiguchi 2014a1	Faldaprevir	1 neutropenia, 3 diarrhoea, 3 nausea, 3 vomiting, 2 influenza-like illness, 8 pyrexia, 2 decreased appetite, 2 arthralgia, 4 dizziness, 1 dysgeusia, 7 headache, 1 depression, 5 insomnia, 1 cough, 3 alopecia, 1 dry skin, 6 pruritus, 6 rash	33 out of 35	2 nausea, 2 vomiting, 1 influenza-like illness, 1 pyrexia, 1 decreased appetite, 1 headache, 1 insomnia, 1 dyspnoea, 2 dry skin, 3 pruritus, 1 rash	6 out of 8

Table 3. Non-serious adverse events *(Continued)*

Sulkowski 2013a	Faldeprevir	85 anaemia, 49 neutropenia, 188 diarrhoea, 239 nausea, 105 vomiting, 122 asthenia, 54 chills, 194 fatigue, 217 influenza-like illness, 82 irritability, 86 pyrexia, 133 decreased appetite, 72 arthralgia, 133 myalgia, 48 dizziness, 25 dysgeusia, 243 headache, 68 depression, 107 insomnia, 100 cough, 73 dyspnoea, 106 alopecia, 122 dry skin, 227 pruritus, 163 rash	620 out of 641	12 anaemia, 8 neutropenia, 13 diarrhoea, 14 nausea, 4 vomiting, 15 asthenia, 8 chills, 24 fatigue, 34 influenza-like illness, 10 irritability, 11 pyrexia, 11 decreased appetite, 5 arthralgia, 12 myalgia, 5 dizziness, 27 headache, 7 depression, 17 insomnia, 9 cough, 11 dyspnoea, 8 alopecia, 10 dry skin, 12 pruritus, 12 rash	65 out of 71
Jacobson 2010	Filibuvir	13 anaemia,4 neutropenia ,6 diarrhoea, 13 nausea, 3 vomiting, 4 chills, 13 fatigue, 3 influenza-like illness, 2 irritability, 2 pyrexia, 3 decreased appetite, 2 arthralgia, 4 myalgia, 4 dizziness, 14 headache, 5 depression, 11 insomnia, 5 cough, 2 dyspnoea, 2 alopecia, 3 dry skin, 2 pruritus, 3 rash	27 out of 27	3 anaemia, 3 diarrhoea, 4 nausea, 1 vomiting, 1 chills, 5 fatigue, 2 influenza-like illness, 2 decreased appetite, 2 arthralgia, 2 headache, 3 depression, 2 insomnia, 2 cough, 2 dyspnoea, 1 alopecia, 2 dry skin, 3 pruritus, 1 rash	8 out of 8
Rodriguez-Torres 2014a1	Filibuvir	26 anaemia, 26 neutropenia, 24 diarrhoea, 55 nausea, 20 vomiting, 35 asthenia, 25 chills, 73 fatigue, 29 influenza-like illness, 33 irritability, 28 pyrexia, 36 decreased appetite, 30 arthralgia, 37 myalgia, 20 dizziness, 40 dysgeusia, 61 headache, 32 depression, 55 insomnia, 33 cough, 18 dyspnoea, 34 alopecia, 33 dry skin, 56 pruritus, 34 rash	174 out of 192	anaemia, neutropenia, diarrhoea, nausea, vomiting, asthenia, chills, fatigue, influenza-like illness, irritability, pyrexia, decreased appetite, arthralgia, myalgia, dizziness, dysgeusia, headache, depression, insomnia, cough, dyspnoea, alopecia, dry skin, pruritus, rash. The authors did not report number of adverse events in the control group	90 out of 96
Petry 2011	Grazoprevir	9 diarrhoea, 2 nausea, 1 vomiting, 7 fatigue, 1 dysgeusia, 16 headache, 1 insomnia, 2 pruritis	34 out of 76	1 headache	2 out of 15
Gardner 2014a	GSK2336805	3 anaemia, 3 neutropenia, 4 nausea, 2 vomiting, 2 chills, 5 fatigue, 2 cough	11 out of 11	1 fatigue	4 out of 4
Lalezari 2012	IDX-184	1 diarrhoea, 2 fatigue, 1 dizziness, 4 headache	8 out of 33	1 diarrhoea, 1 fatigue, 1 dizziness, 1 headache	4 out of 8
Lalezari 2013	IDX-184	6 neutropenia, 7 diarrhoea, 22 nausea, 5 vomiting, 15 chills, 36 fatigue, 10 irritability, 9 pyrexia, 5 decreased appetite, 19 myalgia, 27 headache, 4 depression, 10 insomnia, 6 pruritus	59 out of 65	4 neutropenia, 2 diarrhoea, 3 nausea, 5 chills, 9 fatigue, 4 irritability, 3 decreased appetite, 5 myalgia, 7 headache, 3 depression, 5 insomnia, 2 pruritus	12 out of 16

Table 3. Non-serious adverse events *(Continued)*

De Bruijne 2010a1	IDX320	1 diarrhoea, 1 myalgia, 4 headache	Not specified out of 30	None reported	0 out of 8
Lawitz 2012a	Ledispasvir	2 nausea, 6 headache, 2 rash	18 out of 59	1 nausea	4 out of 11
Gane 2010	Mericitabine/danoprevir	7 diarrhoea, 9 nausea, 36 headache, 9 rash	Not specified out of 73	1 diarrhoea, 2 nausea, 8 headache, 1 rash	Not specified out of 14
Feld 2015	Mericitabine	25 diarrhoea, 16 nausea, 6 chills, 47 fatigue, 14 irritability, 16 pyrexia, 12 arthralgia, 19 myalgia, 43 headache, 27 insomnia, 21 cough, 15 pruritus	Not specified out of 102	12 diarrhoea, 14 nausea, 12 chills, 25 fatigue, 10 irritability, 14 pyrexia, 11 arthralgia, 18 myalgia, 28 headache, 11 insomnia, 11 cough, 11 pruritus	Not specified out of 49
JUMP-C 2013	Mericitabine	18 diarrhoea, 33 nausea, 31 chills, 58 fatigue, 21 irritability, 20 pyrexia, 25 decreased appetite, 18 arthralgia, 24 myalgia, 19 dizziness, 42 headache, 31 insomnia, 17 cough, 14 alopecia, 15 pruritus, 17 rash	Not specified out of 81	20 diarrhoea, 34 nausea, 33 chills, 58 fatigue, 25 irritability, 27 pyrexia, 22 decreased appetite, 21 arthralgia, 24 myalgia, 20 dizziness, 38 headache, 28 insomnia, 22 cough, 17 alopecia, 28 pruritus, 28 rash	Not specified out of 85
De Bruijne 2010a2	Narlaprevir	10 diarrhoea, 8 nausea, 30 influenza-like illness, 6 dizziness, 11 headache	32 out of 32	1 nausea, 6 influenza-like illness, 1 dizziness	7 out of 8
Vierling 2011	Narlaprevir	87 anaemia, 84 diarrhoea, 131 nausea, 54 vomiting, 44 chills, 123 fatigue, 106 influenza-like illness, 58 irritability, 58 pyrexia, 61 decreased appetite, 60 arthralgia, 39 myalgia, 58 dizziness, 83 headache, 33 depression, 80 insomnia, 28 pruritus, 31 rash	Not specified out of 93	6 anaemia, 17 diarrhoea, 50 nausea, 28 vomiting, 17 chills, 56 fatigue, 44 influenza-like illness, 28 irritability, 17 pyrexia, 44 decreased appetite, 28 arthralgia, 6 dizziness, 39 headache, 22 depression, 39 insomnia, 33 pruritus, 11 rash	Not specified out of 18
Muir 2014	Odalasvir/sovaprevir	5 anaemia, 2 diarrhoea, 5 fatigue, 2 influenza-like illness, 2 irritability, 1 decreased appetite, 2 arthralgia, 3 myalgia, 1 dizziness, 1 dysgeusia, 6 headache, 2 insomnia, 4 cough, 1 dyspnoea, 1 pruritus, 1 rash	20 out of 20	2 diarrhoea, 4 fatigue, 1 myalgia, 1 dizziness, 1 headache, 1 cough, pruritus	10 out of 10
Sullivan 2012	Ombitasvir	6 anaemia, 5 neutropenia, 4 diarrhoea, 9 nausea, 7 vomiting, 6 chills, 18 fatigue, 1 influenza-like illness, 1 irritability, 3 pyrexia, 5 decreased appetite, 2 arthralgia, 2 myalgia, 2 dizziness, 9 headache, 4 depression, 4 insomnia, 3 cough, 2 dyspnoea, 5 dry skin, 3 pruritus, 6 rash	26 out of 28	1 neutropenia, 1 diarrhoea, 3 nausea, 2 vomiting, 6 fatigue, 2 influenza-like illness, 1 irritability, 1 decreased appetite, 1 myalgia, 2 headache, 1 depression, 2 insomnia, 1 cough, dyspnoea, 1 dry skin, 2 rash	9 out of 9

Table 3. Non-serious adverse events *(Continued)*

Anderson 2014a1	Paritaprevir/ABT-072/dasabuvir	12 anaemia, 14 neutropenia, 16 diarrhoea, 15 nausea, 6 vomiting, 4 asthenia, 11 chills, 29 fatigue, 14 influenza-like illness, 8 irritability, 12 pyrexia, 4 decreased appetite, 9 arthralgia, 14 myalgia, 9 dizziness, 6 dysgeusia, 38 headache, 15 depression, 14 insomnia, 6 cough, 6 dyspnoea, 5 alopecia, 2 dry skin, 8 pruritus, 12 rash	63 out of 63	1 anaemia, 2 neutropenia, 4 diarrhoea, 4 nausea, 1 vomiting, 1 asthenia, 6 fatigue, 1 influenza-like illness, 1 irritability, 1 pyrexia, 2 decreased appetite, 1 arthralgia, 3 myalgia, 4 dizziness, 2 dysgeusia, 4 headache, 2 insomnia, 2 dyspnoea, 1 alopecia, 2 pruritus, 2 rash	10 out of 11
Feld 2014	Paritaprevir/ombitasvir	24 anaemia, 65 diarrhoea, 112 nausea, 23 vomiting, 59 asthenia, 164 fatigue, 26 irritability, 37 decreased appetite, 23 arthralgia, 21 myalgia, 38 dizziness, 156 headache, 67 insomnia, 34 cough, 38 dyspnoea, 27 dry skin, 80 pruritus, 51 rash	391 out of 473	11 diarrhoea, 22 nausea, 6 vomiting, 6 asthenia, 45 fatigue, 4 irritability, 5 decreased appetite, 9 arthralgia, 8 myalgia, 6 dizziness, 42 headache, 12 insomnia, 8 cough, 4 dyspnoea, 2 dry skin, 7 pruritus, 9 rash	108 out of 158
Zeuzem 2014a	Paritaprevir/ombitasvir	19 anaemia, 47 diarrhoea, 72 nausea, 22 vomiting, 60 asthenia, 115 fatigue, 22 irritability, 24 decreased appetite, 21 arthralgia, 28 myalgia, 30 dizziness, 13 dysgeusia, 126 headache, 52 insomnia, 43 cough, 50 dyspnoea, 27 dry skin, 53 pruritus, 34 rash	328 out of 394	12 diarrhoea, 17 nausea, 11 asthenia, 22 fatigue, 8 irritability, 2 decreased appetite, 7 arthralgia, 10 myalgia, 5 dizziness, 5 dysgeusia, 34 headache, 7 insomnia, 5 cough, 10 dyspnoea, 3 dry skin, 5 pruritus, 6 rash	74 out of 97
Hotho 2012	PHX1766	1 nausea, 2 fatigue, 1 dizziness	Not specified	None reported	Not specified
Pockros 2008a1	R1626	43 neutropenia, 42 diarrhoea, 49 nausea, 26 vomiting, 39 chills, 45 fatigue, 20 irritability, 29 pyrexia, 21 arthralgia, 23 myalgia, 15 dizziness, 47 headache, 27 insomnia, 15 cough, 11 pruritus, 20 rash	Not specified out of 84	5 diarrhoea, 10 nausea, 2 vomiting, 9 chills, 10 fatigue, 1 irritability, 8 pyrexia, 5 arthralgia, 11 myalgia, 3 dizziness, 11 headache, 6 insomnia, 4 cough, 6 pruritus, 2 rash	Not specified out of 20
Vince 2014	Samatasvir	4 nausea, 1 decreased appetite, 6 headache, 1 insomnia	20 out of 48	1 nausea, 1 decreased appetite, 1 headache, 1 insomnia	6 out of 12
Forns 2014	Simeprevir	40 anaemia, 37 neutropenia, 36 diarrhoea, 59 nausea, 18 vomiting, 57 asthenia, 17 chills, 87 fatigue, 78 influenza-like illness, 63 pyrexia, 35 decreased appetite, 26 arthralgia, 39 myalgia, 14 dizziness, 12 dysgeusia, 87 headache, 22 depression, 49 insomnia, 34 cough, 26 dyspnoea, 26 alopecia, 24 dry skin, 16 pruritus, 33 rash	245 out of 260	24 anaemia, 26 neutropenia, 22 diarrhoea, 26 nausea, 9 vomiting, 25 asthenia, 11 chills, 58 fatigue, 27 influenza-like illness, 30 pyrexia, 24 decreased appetite, 12 arthralgia, 17 myalgia, 6 dizziness, 7 dysgeusia, 48 headache, 10 depression, 33 insomnia, 21 cough, 5 dyspnoea, 17 alopecia, 18 dry skin, 37 pruritus, 19 rash	123 out of 133

Table 3. Non-serious adverse events *(Continued)*

Fried 2013	Simeprevir	63 anaemia, 75 neutropenia, 47 diarrhoea, 86 nausea, 22 vomiting, 63 asthenia, 25 chills, 107 fatigue, 98 influenza-like illness, 11 irritability, 64 pyrexia, 17 decreased appetite, 53 arthralgia, 55 myalgia, 29 dizziness, 16 dysgeusia, 142 headache, 32 depression, 69 insomnia, 52 cough, 33 dyspnoea, 53 alopecia, 63 dry skin, 173 pruritus, 65 rash	302 out of 309	16 anaemia, 16 neutropenia, 12 diarrhoea, 21 nausea, 5 vomiting, 16 asthenia, 8 chills, 37 fatigue, 29 influenza-like illness, 8 irritability, 13 pyrexia, 6 decreased appetite, 11 arthralgia, 17 myalgia, 6 dizziness, 5 dysgeusia, 40 headache, 14 depression, 23 insomnia, 15 cough, 6 dyspnoea, 16 alopecia, 14 dry skin, 35 pruritus, 18 rash	75 out of 77
DRAGON 2014a1	Simeprevir	24 anaemia, 13 diarrhoea,13 nausea, 6 vomiting, 4 chills, 2 fatigue, 42 pyrexia, 15 decreased appetite, 27 arthralgia, 15 myalgia, 3 dizziness, 6 dysgeusia, 41 headache, 2 depression, 23 insomnia, 8 cough, 25 alopecia, 5 dry skin, 15 pruritus, 47 rash	79 out of 79	5 anaemia, 5 diarrhoea, 2 vomiting, 7 pyrexia, 3 decreased appetite, 2 arthralgia, 2 myalgia, 8 headache, 2 insomnia, 2 cough, 6 alopecia, 6 rash	13 out of 13
CONCERTO-1 2015	Simeprevir	70 anaemia, 8 neutropenia, 20 diarrhoea, 16 nausea, 6 vomiting, 13 fatigue, 75 pyrexia, 28 decreased appetite, 30 arthralgia, 9 myalgia, 4 dizziness, 20 dysgeusia, 54 headache, 27 insomnia, 11 cough, 44 alopecia, 8 dry skin, 35 pruritus, 57 rash	123 out of 123	36 anaemia, 1 neutropenia, 20 diarrhoea, 16 nausea, 6 vomiting, 7 fatigue, 31 pyrexia, 20 decreased appetite, 14 arthralgia, 11 myalgia, 4 dizziness, 8 dysgeusia, 26 headache, 3 depression, 25 insomnia, 8 cough, 28 alopecia, 9 dry skin, 18 pruritus, 37 rash	60 out of 60
Hoeben 2015a1	Simeprevir	82 anaemia, 59 neutropenia, 14 diarrhoea, 16 nausea, 15 asthenia, 63 fatigue, 39 influenza-like illness, 67 pyrexia, 28 decreased appetite, 13 arthralgia, 36 myalgia, 39 headache, 17 insomnia, 16 cough, 47 alopecia, 40 pruritus, 57 rash	298 out of 305	53 anaemia, 32 neutropenia, 7 diarrhoea, 10 nausea, 7 asthenia, 36 fatigue, 19 influenza-like illness, 46 pyrexia, 16 decreased appetite, 4 arthralgia, 22 myalgia, 28 headache, 18 insomnia, 17 cough, 26 alopecia, 17 pruritus, 27 rash	149 out of 152
Jacobson 2014	Simeprevir	44 anaemia, 54 neutropenia, 35 diarrhoea, 65 nausea, 23 vomiting, 25 asthenia, 33 chills, 111 fatigue, 62 influenza-like illness, 51 pyrexia, 47 decreased appetite, 34 arthralgia, 39 myalgia, 23 dizziness, 16 dysgeusia, 88 headache, 23 depression, 56 insomnia, 25 cough, 23 dyspnoea, 30 alopecia, 33 dry skin, 68 pruritus, 60 rash	252 out of 264	24 anaemia, 15 neutropenia, 19 diarrhoea, 32 nausea, 9 vomiting, 21 asthenia, 18 chills, 53 fatigue, 26 influenza-like illness, 28 pyrexia, 19 decreased appetite, 21 arthralgia, 18 myalgia, 9 dizziness, 4 dysgeusia, 51 headache, 16 depression, 31 insomnia, 20 cough, 9 dyspnoea, 16 alopecia, 11 dry skin, 20 pruritus, 30 rash	124 out of 130

Table 3. Non-serious adverse events *(Continued)*

OPERA 2011a1	Simeprevir	16 anaemia, 26 neutropenia, 20 diarrhoea, 31 nausea, 9 vomiting, 26 asthenia, 6 chills, 35 fatigue, 24 influenza-like illness, 10 irritability, 21 pyrexia, 7 decreased appetite, 20 arthralgia, 14 myalgia, 4 dizziness, 5 dysgeusia, 42 headache, 14 depression, 12 insomnia, 19 cough, 18 dyspnoea, 16 alopecia, 19 dry skin, 18 pruritus, 9 rash	82 out of 83	4 anaemia, 4 neutropenia, 3 diarrhoea, 4 nausea, 3 vomiting, 7 asthenia, 5 chills, 13 fatigue, 5 influenza-like illness, 4 irritability, 4 pyrexia, 2 decreased appetite, 3 arthralgia, 8 myalgia, 3 dizziness, 3 dysgeusia, 16 headache, 2 depression, 7 insomnia, 10 cough, 4 dyspnoea, 3 alopecia, 5 dry skin, 7 pruritus, 5 rash	28 out of 28
Manns 2014a	Simeprevir	46 anaemia, 49 neutropenia, 34 diarrhoea, 63 nausea, 17 vomiting, 59 asthenia, 21 chills, 95 fatigue, 66 influenza-like illness, 80 pyrexia, 46 decreased appetite, 32 arthralgia, 58 myalgia, 21 dizziness, 101 headache, 29 depression, 51 insomnia, 32 cough, 23 dyspnoea, 43 alopecia, 28 dry skin, 65 pruritus, 46 rash	243 out of 257	33 anaemia, 29 neutropenia, 12 diarrhoea, 24 nausea, 7 vomiting, 38 asthenia, 12 chills, 56 fatigue, 35 influenza-like illness, 53 pyrexia, 21 decreased appetite, 14 arthralgia, 28 myalgia, 9 dizziness, 49 headache, 19 depression, 21 insomnia, 22 cough, 11 dyspnoea, 27 alopecia, 18 dry skin, 34 pruritus, 15 rash	131 out of 134
Pearlman 2015	Simeprevir	1 anaemia, 1 diarrhoea, 6 nausea, 8 fatigue, 1 irritability, 2 myalgia, 7 headache, 3 insomnia, 6 pruritus, 10 rash	46 out of 58	9 anaemia, 5 neutropenia, 2 diarrhoea, 7 nausea, 4 asthenia, 17 fatigue, 6 influenza-like illness, 3 irritability, 4 myalgia, 8 headache, 6 insomnia, 4 pruritus, 3 rash	22 out of 24
ASPIRE 2014	Simeprevir	76 anaemia, 101 neutropenia, 59 diarrhoea, 95 nausea, 21 vomiting, 84 asthenia, 34 chills, 174 fatigue, 116 influenza-like illness, 53 irritability, 69 pyrexia, 69 decreased appetite, 50 arthralgia, 64 myalgia, 29 dizziness, 22 dysgeusia, 138 headache, 45 depression, 79 insomnia, 76 cough, 49 dyspnoea, 31 alopecia, 72 dry skin, 135 pruritus, 61 rash	380 out of 396	13 anaemia, 11 neutropenia, 13 diarrhoea, 14 nausea, 5 vomiting, 7 asthenia, 6 chills, 174 fatigue, 13 influenza-like illness, 7 irritability, 9 pyrexia, 9 decreased appetite, 9 arthralgia, 12 myalgia, 6 dizziness, 3 dysgeusia, 24 headache, 6 depression, 9 insomnia, 8 cough, 4 dyspnoea, 5 alopecia, 10 dry skin, 11 pruritus, 9 rash	63 out of 66
Jacobson 2014	Sofosbuvir	19 diarrhoea, 46 nausea, 12 vomiting, 91 fatigue, 19 irritability, 7 decreased appetite, 16 arthralgia, 19 dizziness, 43 headache, 15 depression, 39 insomnia, 11 cough, 19 dyspnoea, 23 pruritus, 18 rash	184 out of 207	4 diarrhoea, 13 nausea, 5 vomiting, 17 fatigue, 1 irritability, 7 decreased appetite, 1 arthralgia, 5 dizziness, 14 headache, 1 depression, 3 insomnia, 2 cough, 1 dyspnoea, 6 pruritus, 6 rash	55 out of 71
Lawitz 2013a1	Sofosbuvir	19 anaemia, 23 neutropenia, 18 diarrhoea, 38 nausea, 12 vomiting, 2 asthenia, 37	117 out of 120	7 anaemia, 5 neutropenia, 2 diarrhoea, 9 nausea, 2 vomiting, 1 asthenia, 10	26 out of 26

Table 3. Non-serious adverse events *(Continued)*

		chills, 64 fatigue, 15 irritability, 22 pyrexia, 11 decreased appetite, 10 arthralgia, 17 myalgia, 11 dizziness, 9 dysgeusia, 37 headache, 12 depression, 24 insomnia, 14 cough, 11 dyspnoea, 10 alopecia, 12 dry skin, 13 pruritus, 29 rash		chills, 16 fatigue, 5 irritability, 2 pyrexia, 4 decreased appetite, 5 arthralgia, 6 myalgia, 3 dizziness, 15 headache, 3 depression, 9 insomnia, 3 cough, 4 dyspnoea, 2 alopecia, 3 dry skin, 3 pruritus, 4 rash	
)FISSION 2013	Sofosbuvir	20 anaemia, 23 diarrhoea, 46 nausea, 17 vomiting, 7 chills, 92 fatigue, 7 influenza-like illness, 25 irritability, 6 pyrexia, 17 decreased appetite, 15 arthralgia, 21 myalgia, 27 dizziness, 64 headache, 14 depression, 31 insomnia, 19 cough, 18 dyspnoea, 12 alopecia, 11 dry skin, 19 pruritus, 23 rash	219 out of 256	28 anaemia, 30 neutropenia, 45 diarrhoea, 70 nausea, 23 vomiting, 44 chills, 134 fatigue, 44 influenza-like illness, 40 irritability, 33 pyrexia, 44 decreased appetite, 35 arthralgia, 40 myalgia, 33 dizziness, 108 headache, 34 depression, 71 insomnia, 21 cough, 20 dyspnoea, 24 alopecia, 23 dry skin, 42 pruritus, 43 rash	233 out of 243
Rodriguez-Torres 2013	Sofosbuvir	7 anaemia, 17 nausea, 3 vomiting, 22 fatigue, 4 pyrexia, 7 decreased appetite, 12 arthralgia, 7 myalgia, 6 dizziness, 15 headache, 4 depression, 7 insomnia, 9 pruritus	45 out of 49	1 anaemia, 5 nausea, 2 chills, 6 fatigue, 1 pyrexia, 1 decreased appetite, 1 myalgia, 2 dizziness, 2 headache, 2 insomnia,1 pruritus	13 out of 14
Feld 2015	Sofosbuvir/velpatasvir	48 diarrhoea, 75 nausea, 41 asthenia, 126 fatigue, 40 arthralgia, 25 myalgia, 182 headache, 50 insomnia, 39 cough	485 out of 624	8 diarrhoea, 13 nausea, 9 asthenia, 23 fatigue, 9 arthralgia, 6 myalgia, 33 headache, 11 insomnia, 4 cough	89 out of 116
3Benhamou 2013a1	Telaprevir	1 diarrhoea, 4 nausea, 1 vomiting, 6 asthenia, 4 fatigue, 10 influenza-like illness, 3 headache, 2 insomnia, 1 dyspnoea, 1 dry skin, 3 pruritus	16 out of 16	1 anaemia, 1 neutropenia, 3 asthenia, 4 influenza-like illness, 1 decreased appetite, 1 headache, 1 insomnia, 1 cough, 1 dry skin, 2 pruritus, 2 rash	8 out of 8
Forestier 2007	Telaprevir	2 diarrhoea, 3 nausea, 1 chills, 5 myalgia, 2 dizziness, 5 headache, 3 dry skin, 3 rash	14 out of 16	1 diarrhoea, 1 nausea, 1 asthenia, 2 chills, 2 myalgia, 1 dizziness, 2 headache, 1 dry skin	4 out of 4
1Foster 2011a1	Telaprevir	1 anaemia, 4 diarrhoea, 8 nausea, 5 vomiting, 9 asthenia, 1 chills, 5 fatigue, 11 influenza-like illness, 1 irritability, 2 pyrexia, 1 arthralgia, 4 myalgia, 3 dizziness, 5 headache, 1 depression, 2 insomnia, 1 cough, 2 dyspnoea, 1 alopecia, 3 dry skin, 11 pruritus, 5 rash	26 out of 31	1 neutropenia, 1 diarrhoea, 1 nausea, 5 asthenia, 3 chills, 2 fatigue, 7 influenza-like illness, 5 pyrexia, 3 myalgia, 1 dysgeusia, 6 headache, 1 depression, 2 insomnia, 2 cough, 2 dyspnoea, 1 dry skin, 2 pruritus	16 out of 18
Hezode 2009	Telaprevir	44 anaemia, 11 neutropenia, 66 diarrhoea, 102 nausea, 22 vomiting, 110 asthenia, 12	240 out of 241	14 anaemia, 14 neutropenia, 23 diarrhoea, 33 nausea, 12 vomiting, 26 asthe-	81 out of 82

Table 3. Non-serious adverse events *(Continued)*

		chills, 70 fatigue, 92 influenza-like illness, 22 irritability, 44 pyrexia, 30 decreased appetite, 36 arthralgia, 35 myalgia, 12 dizziness, 20 dysgeusia, 105 headache, 51 depression, 62 insomnia, 37 cough, 50 dyspnoea, 29 alopecia, 64 dry skin, 139 pruritus, 71 rash		nia, 10 chills, 30 fatigue, 43 influenza-like illness, 11 irritability, 19 pyrexia, 16 decreased appetite, 14 arthralgia, 17 myalgia, 8 dizziness, 3 dysgeusia, 37 headache, 19 depression, 32 insomnia, 21 cough, 13 dyspnoea, 17 alopecia, 29 dry skin, 29 pruritus, 22 rash	
Jacobson 2010	Telaprevir	276 anaemia, 217 diarrhoea, 302 nausea, 418 fatigue, 203 pyrexia, 304 headache, 233 insomnia, 346 pruritus, 262 rash	723 out of 727	70 anaemia, 80 diarrhoea, 112 nausea, 206 fatigue, 87 pyrexia, 142 headache, 111 insomnia, 131 pruritus, 88 rash	354 out of 361
McHutchison 2009	Telaprevir	58 anaemia, 30 neutropenia, 64 diarrhoea, 93 nausea, 38 vomiting, 29 chills, 127 fatigue, 75 influenza-like illness, 23 irritability, 33 pyrexia, 22 decreased appetite, 34 arthralgia, 27 myalgia, 41 dizziness, 16 dysgeusia, 80 headache, 34 depression, 68 insomnia, 36 cough, 25 dyspnoea, 21 alopecia, 28 dry skin, 74 pruritus, 62 rash	175 out of 175	20 anaemia, 18 neutropenia, 21 diarrhoea, 22 nausea, 9 vomiting, 14 chills, 57 fatigue, 32 influenza-like illness, 22 irritability, 22 pyrexia, 9 decreased appetite, 16 arthralgia, 18 myalgia, 14 dizziness, 8 dysgeusia, 45 headache, 13 depression, 29 insomnia, 14 cough, 11 dyspnoea, 8 alopecia, 19 dry skin, 17 pruritus, 20 rash	75 out of 75
McHutchison 2010	Telaprevir	69 anaemia, 31 neutropenia, 115 diarrhoea, 122 nausea, 37 vomiting, 57 chills, 197 fatigue, 93 influenza-like illness, 63 irritability, 59 pyrexia, 20 decreased appetite, 51 arthralgia, 60 myalgia, 47 dizziness, 130 headache, 43 depression, 83 insomnia, 46 cough, 27 dyspnoea, 54 alopecia, 32 dry skin, 129 pruritus, 126 rash	329 out of 339	9 anaemia, 7 neutropenia, 22 diarrhoea, 39 nausea, 13 vomiting, 15 chills, 64 fatigue, 36 influenza-like illness, 25 irritability, 14 pyrexia, 12 decreased appetite, 21 arthralgia, 21 myalgia, 18 dizziness, 41 headache, 19 depression, 19 insomnia, 20 cough, 9 dyspnoea, 13 alopecia, 7 dry skin, 17 pruritus, 20 rash	111 out of 114
Sulkowski 2013a	Telaprevir	35 anaemia, 26 neutropenia, 34 diarrhoea, 44 nausea, 27 vomiting, 22 asthenia, 15 chills, 50 fatigue, 24 influenza-like illness, 18 irritability, 34 pyrexia, 30 decreased appetite, 9 arthralgia, 20 myalgia, 19 dizziness, 18 dysgeusia, 38 headache, 11 depression, 25 insomnia, 15 cough, 5 dyspnoea, 18 alopecia, 11 dry skin, 30 pruritus, 12 rash	38 out of 38	8 anaemia, 2 neutropenia, 6 diarrhoea, 11 nausea, 5 vomiting, 9 asthenia, 5 chills, 12 fatigue, 13 influenza-like illness, 5 irritability, 7 pyrexia, 6 decreased appetite, 2 arthralgia, 6 myalgia, 2 dizziness, 5 dysgeusia, 6 headache, 4 depression, 9 insomnia, 6 cough, 2 dyspnoea, 6 alopecia, 3 dry skin, 3 pruritus	22 out of 22
Zeuzem 2011a	Telaprevir	171 anaemia, 73 neutropenia, 135 diarrhoea, 181 nausea, 68 vomiting, 111 asthenia, 73	517 out of 530	19 anaemia, 14 neutropenia, 18 diarrhoea, 31 nausea, 11 vomiting, 38 asthe-	126 out of 132

Table 3. Non-serious adverse events *(Continued)*

		chills, 276 fatigue, 179 influenza-like illness, 74 irritability, 130 pyrexia, 40 decreased appetite, 67 arthralgia, 87 myalgia, 47 dizziness, 65 dysgeusia, 221 headache, 59 depression, 152 insomnia, 128 cough, 82 dyspnoea, 78 alopecia, 97 dry skin, 270 pruritus, 194 rash		nia, 73 chills, 53 fatigue, 33 influenza-like illness, 21 irritability, 36 pyrexia, 9 decreased appetite, 20 arthralgia, 24 myalgia, 7 dizziness, 8 dysgeusia, 49 headache, 19 depression, 34 insomnia, 26 cough, 17 dyspnoea, 17 alopecia, 21 dry skin, 36 pruritus, 25 rash	
Lawitz 2013a1	Vaniprevir	6 anaemia, 7 neutropenia, 16 diarrhoea, 26 nausea, 16 vomiting, 13 asthenia, 5 chills, 17 fatigue, 17influenza-like illness, 4 irritability, 8 pyrexia, 13 decreased appetite, 8 arthralgia, 3 myalgia, 5 dizziness, 2 dysgeusia, 26 headache, 8 depression, 15 insomnia, 8 cough, 7 dyspnoea, 6 alopecia, 6 dry skin, 9 pruritus, 10 rash	71 out of 75	3 anaemia, 2 neutropenia, 4 diarrhoea, 6 nausea, 4 asthenia, 2 chills, 7 fatigue, 4 influenza-like illness, 3 irritability, 2 pyrexia, 2 decreased appetite, 2 arthralgia, 3 myalgia, 7 headache, 3 depression, 2 insomnia, 3 cough, 5 dyspnoea, 3 alopecia, 6 dry skin, 4 pruritus, 4 rash	19 out of 19
Manns 2012a1	Vaniprevir	6 anaemia, 7 neutropenia, 16 diarrhoea, 26 nausea, 16 vomiting, 13 asthenia, 5 chills, 17 fatigue, 17 influenza-like illness, 4 irritability, 8 pyrexia, 13 decreased appetite, 8 arthralgia, 3 myalgia, 5 dizziness, 2 dysgeusia, 26 headache, 8 depression, 15 insomnia, 8 cough, 7 dyspnoea, 6 alopecia, 6 dry skin, 9 pruritus, 10 rash	71 out of 75	3 anaemia, 2 neutropenia, 4 diarrhoea, 6 nausea, 4 asthenia, 2 chills, 7 fatigue, 4 influenza-like illness, 3 irritability, 2 pyrexia, 2 decreased appetite, 2 arthralgia, 3 myalgia, 7 headache, 3 depression, 2 insomnia, 3 cough, 5 dyspnoea, 3 alopecia, 6 dry skin, 4 pruritus, 4 rash	19 out of 19
Rodriguez-Torres 2014a1	Vaniprevir	43 anaemia, 34 neutropenia, 97 diarrhoea, 110 nausea, 59 vomiting, 50 asthenia, 16 chills, 92 fatigue, 54 influenza-like illness, 24 irritability, 37 pyrexia, 40 decreased appetite, 37 arthralgia, 38 myalgia, 23 dizziness, 16 dysgeusia, 92 headache, 32 depression, 40 insomnia, 54 cough, 30 dyspnoea, 35 alopecia, 37 dry skin, 75 pruritus, 43 rash	225 out of 229	8 anaemia, 3 neutropenia, 9 diarrhoea, 10 nausea, 3 vomiting, 11 asthenia, 1 chills, 18 fatigue, 12 influenza-like illness, 8 irritability, 14 pyrexia, 5 decreased appetite, 11 arthralgia, 12 myalgia, 6 dizziness, 3 dysgeusia, 20 headache, 3 depression, 14 insomnia, 14 cough, 8 dyspnoea, 5 alopecia, 10 dry skin, 14 pruritus, 10 rash	55 out of 56
Lawitz 2013c	Vaniprevir	43 anaemia, 34 neutropenia, 97 diarrhoea, 110 nausea, 59 vomiting, 50 asthenia, 16 chills, 92 fatigue, 54 influenza-like illness, 24 irritability, 37 pyrexia, 40 decreased appetite, 37 arthralgia, 38 myalgia, 23 dizziness, 16 dysgeusia, 92 headache, 32 depression, 40 insomnia, 54 cough,	225 out of 229	8 anaemia, 3 neutropenia, 9 diarrhoea, 10 nausea, 3 vomiting, 11 asthenia, 1 chills, 18 fatigue, 12 influenza-like illness, 8 irritability, 14 pyrexia, 5 decreased appetite, 11 arthralgia, 12 myalgia, 6 dizziness, 3 dysgeusia, 20 headache, 3 depression, 14 insomnia, 14 cough, 8 dyspnoea, 5 alope-	55 out of 56

Table 3. Non-serious adverse events *(Continued)*

		30 dyspnoea, 35 alopecia, 37 dry skin, 75 pruritus, 43 rash		cia, 10 dry skin, 14 pruritus, 10 rash	
Cooper 2009	VCH-759	18 diarrhoea, 3 nausea, 4 vomiting, 1 chills, 5 fatigue, 8 headache	20 out of 23	5 diarrhoea, 1 nausea, 2 headache	6 out of 9
Lawitz 2015	Velpatasvir	2 diarrhoea, 3 nausea, 4 vomiting, 6 headache, 2 cough	18 out of 70	None reported	3 out of 17

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	28 October 2016	direct*acting antiviral* or DAA* or ((protease or polymerase) and inhibitor*) or telaprevir or boceprevir or simeprevir or paritaprevir or faldaprevir or asunaprevir or grazoprevir or sovaprevir or danoprevir or vedroprevir or vaniprevir or narlaprevir or sofosbuvir or dasabuvir or beclabuvir or deleobuvir or filibuvir or setrobuvir or radalbuvir or tegobuvir or ledipasvir or ombitasvir or declatasvir or elbasvir or odalasvir or samatasvir or ravidasvir or mericitabine or incivek or incivo or telavic or sunpreva or victrelis or INN or olysio or sovriad or galexos or viekira* or technivie or NPI* or harvoni or daklinza or sovaldi or exviera or USAN* or VX*135 or VX*222 or VX*950 or ABT*072 or ABT*450 or TMC*647055 or TMC*435 or GSK*2336805 or GS*9256 or GS*5885 or PPI*461 or BI*201127 or INX*189 or BMS*986094 or BMS*790052 and (chronic and (hepatitis C or hep C or HCV))
Cochrane Central Register of Controlled Trials (Wiley)	2016, Issue 9	#1 MeSH descriptor: [Antiviral Agents] explode all trees #2 MeSH descriptor: [Protease Inhibitors] explode all trees #3 MeSH descriptor: [Nucleic Acid Synthesis Inhibitors] explode all trees #4 direct*acting antiviral* or DAA* or ((protease or polymerase) and inhibitor*) or telaprevir or boceprevir or simeprevir or paritaprevir or faldaprevir or asunaprevir or grazoprevir or sovaprevir or danoprevir or vedroprevir or vaniprevir or narlaprevir or sofosbuvir or dasabuvir or beclabuvir or deleobuvir or filibuvir or setrobuvir or radalbuvir or tegobuvir or ledipasvir or ombitasvir or declatasvir or elbasvir or odalasvir or samatasvir or ravidasvir or mericitabine or incivek or incivo or telavic or sunpreva or victrelis or INN or olysio or sovriad or galexos or viekira* or technivie or NPI* or harvoni or daklinza or sovaldi or exviera or USAN* or VX*135 or VX*222 or VX*950 or ABT*072 or ABT*450 or TMC*647055 or TMC*435 or GSK*2336805 or GS*9256 or GS*5885 or PPI*461 or BI*201127 or INX*189 or BMS*986094 or BMS*790052 #5 #1 or #2 or #3 or #4 #6 MeSH descriptor: [Hepatitis C, Chronic] explode all trees #7 chronic and (hepatitis C or hep C or HCV) #8 #6 or #7 #9 #5 and #8
MEDLINE (OvidSP)	1946 to 28 October 2016	1. exp Antiviral Agents/ 2. exp Protease Inhibitors/ 3. exp Nucleic Acid Synthesis Inhibitors/ 4. (direct*acting antiviral* or DAA* or ((protease or polymerase) and inhibitor*) or telaprevir or boceprevir or simeprevir or paritaprevir or faldaprevir or

(Continued)

		asunaprevir or grazoprevir or sovaprevir or danoprevir or vedroprevir or vaniprevir or narlaprevir or sofosbuvir or dasabuvir or beclabuvir or deleobuvir or filibuvir or setrobuvir or radalbuvir or tegobuvir or ledipasvir or ombitasvir or declatasvir or elbasvir or odalasvir or samatasvir or ravidasvir or mericitabine or incivek or incivo or telavic or sunpreva or victrelis or INN or olysio or sovriad or galexos or viekira* or technivie or NPI* or harvoni or daklinza or sovaldi or exviera or USAN* or VX*135 or VX*222 or VX*950 or ABT*072 or ABT*450 or TMC*647055 or TMC*435 or GSK*2336805 or GS*9256 or GS*5885 or PPI*461 or BI*201127 or INX*189 or BMS*986094 or BMS*790052).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. 1 or 2 or 3 or 4 6. exp Hepatitis C, Chronic/ 7. (chronic and (hepatitis C or hep C or HCV)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 8. 6 or 7 9. 5 and 8 10. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 11. 9 and 10
Embase (Ovid SP)	1974 to 28 October 2016	1. exp antivirus agent/ 2. exp proteinase inhibitor/ 3. exp nucleic acid synthesis inhibitor/ 4. (direct*acting antiviral* or DAA* or ((protease or polymerase) and inhibitor*) or telaprevir or boceprevir or simeprevir or paritaprevir or faldaprevir or asunaprevir or grazoprevir or sovaprevir or danoprevir or vedroprevir or vaniprevir or narlaprevir or sofosbuvir or dasabuvir or beclabuvir or deleobuvir or filibuvir or setrobuvir or radalbuvir or tegobuvir or ledipasvir or ombitasvir or declatasvir or elbasvir or odalasvir or samatasvir or ravidasvir or mericitabine or incivek or incivo or telavic or sunpreva or victrelis or INN or olysio or sovriad or galexos or viekira* or technivie or NPI* or harvoni or daklinza or sovaldi or exviera or USAN* or VX*135 or VX*222 or VX*950 or ABT*072 or ABT*450 or TMC*647055 or TMC*435 or GSK*2336805 or GS*9256 or GS*5885 or PPI*461 or BI*201127 or INX*189 or BMS*986094 or BMS*790052).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 5. 1 or 2 or 3 or 4 6. exp chronic hepatitis C/ 7. (chronic and (hepatitis C or hep C or HCV)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 8. 6 or 7 9. 5 and 8 10. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 11. 9 and 10
Science Citation Index Expanded (Web of Science)	1900 to 28 October 2016	#5 #4 AND #3 #4 TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=(chronic and (hepatitis C or hep C or HCV)) #1 TS=(direct*acting antiviral* or DAA* or ((protease or polymerase) and inhibitor*) or telaprevir or boceprevir or simeprevir or paritaprevir or faldaprevir

(Continued)

		or asunaprevir or grazoprevir or sovaprevir or danoprevir or vedroprevir or vaniprevir or narlaprevir or sofosbuvir or dasabuvir or beclabuvir or deleobuvir or filibuvir or setrobuvir or radalbuvir or tegobuvir or ledipasvir or ombitasvir or declatasvir or elbasvir or odalasvir or samatasvir or ravidasvir or mericitabine or incivek or incivo or telavic or sunpreva or victrelis or INN or olysio or sovriad or galexos or viekira* or technivie or NPI* or harvoni or daklinza or sovaldi or exviera or USAN* or VX*135 or VX*222 or VX*950 or ABT*072 or ABT*450 or TMC*647055 or TMC*435 or GSK*2336805 or GS*9256 or GS*5885 or PPI*461 or BI*201127 or INX*189 or BMS*986094 or BMS*790052)
LILACS (Bireme)	1982 to 28 October 2016	(chronic and (hepatitis C or hep C or HCV)) [Words] and ((antiviral$ or DAA$ or ((protease or polymerase) and inhibitor$)) or (telaprevir or boceprevir or simeprevir or paritaprevir or faldaprevir or asunaprevir or grazoprevir or sovaprevir or danoprevir or vedroprevir or vaniprevir or narlaprevir or sofosbuvir or dasabuvir or beclabuvir or deleobuvir or filibuvir or setrobuvir or radalbuvir or tegobuvir or ledipasvir or ombitasvir or declatasvir or elbasvir or odalasvir or samatasvir or ravidasvir or mericitabine or incivek or incivo or telavic or sunpreva or victrelis or INN or olysio or sovriad or galexos or viekira$ or technivie or NPI$ or harvoni or daklinza or sovaldi or exviera or USAN$ or VX$135 or VX$222 or VX$950 or ABT$072 or ABT$450 or TMC$647055 or TMC$435 or GSK $2336805 or GS$9256 or GS$5885 or PPI$461 or BI$201127 or INX$189 or BMS $986094 or BMS$790052)) [Words]
BIOSIS (Web of Science)	1969 to 28 October 2016	#5 #4 AND #3 #4 TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=(chronic and (hepatitis C or hep C or HCV)) #1 TS=(direct*acting antiviral* or DAA* or ((protease or polymerase) and inhibitor*) or telaprevir or boceprevir or simeprevir or paritaprevir or faldaprevir or asunaprevir or grazoprevir or sovaprevir or danoprevir or vedroprevir or vaniprevir or narlaprevir or sofosbuvir or dasabuvir or beclabuvir or deleobuvir or filibuvir or setrobuvir or radalbuvir or tegobuvir or ledipasvir or ombitasvir or declatasvir or elbasvir or odalasvir or samatasvir or ravidasvir or mericitabine or incivek or incivo or telavic or sunpreva or victrelis or INN or olysio or sovriad or galexos or viekira* or technivie or NPI* or harvoni or daklinza or sovaldi or exviera or USAN* or VX*135 or VX*222 or VX*950 or ABT*072 or ABT*450 or TMC*647055 or TMC*435 or GSK*2336805 or GS*9256 or GS*5885 or PPI*461 or BI*201127 or INX*189 or BMS*986094 or BMS*790052)

FEEDBACK

Direct-acting antivirals for chronic hepatitis C, 7 July 2017

Summary

I have formerly held positions as the Associate Editor of Clinical Infectious Diseases for Viral Hepatitis, Deputy Editor of UpToDate and panelist on the HCV treatment guidelines for the Department of Health and Human Services so I am very familiar with the importance of GRADE and proper weighting of evidence. I was also a former clinician who devoted myself to the treatment of HIV and HCV but am no longer seeing patients.

I was distressed to read the recent review you published on the clinical implications of hepatitis C treatment with DAAs. Suffice it to say that the recent response by Anna Lok (AASLD) and William Powderly (IDSA) clearly outline the folly of the conclusions of this paper.

It reminded me of another Cochrane review on efavirenz for the treatment of HIV that was misguided and eventually retracted after massive protests from many readers (including myself).

Over the many years I worked at UpToDate I have read many Cochrane reviews, several of which were outstanding papers that I incorporated into the program. However, I would strongly recommend that you always have one expert clinician without industry ties to be a co-author on any of your reviews since all of the authors on the current HCV paper have written on a potpourri of topics, but none is

a clinical expert on the topic at hand. Your authors have completely missed the mark with this review and sadly, have likely caused harm on the progress in the field.

Cochrane has the logo "Trusted Evidence, Informed Decisions, Better Health". Read the public outcry and blossoming number of editorials of condemnation by top experts in the field worldwide. I strongly urge you to consider retraction of this misguided paper.

Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?

I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment. Currently, I work at Seres Therapeutics in Cambridge, Massachusetts in the area of Medical Affairs. Seres Therapeutics is working on drugs for the treatment of Clostridium difficile and ulcerative colitis, so I do not have any conflicts of interest in the area of hepatitis C therapeutics.

Contributor: Barbara McGovern.

Reply

We thank Barbara McGovern for showing an interest in our systematic review on direct acting antivirals (DAAs) for people with chronic hepatitis C.

We are sorry to learn that our review has caused distress. However, we think that it is necessary to point out the limitations we have found with the current evidence base. We do not yet have sufficiently convincing evidence from randomised clinical trials that short term sustained virological response (SVR) translates in to long term cure. Decisions to use the new DAAs should consider the status of SVR as a surrogate for cure.

With regard to the question of authorship, we believe that the composition of the author team does indeed reflect appropriate clinical expertise. Our author group includes seven specialists in gastroenterology/hepatology, five of whom are in clinic on a daily basis. One of the authors (RLK) has had a career-long interest in hepatitis C and has been writing papers, book chapters, and editorials on this topic for decades, dating back to the original discovery of non-A, non-B hepatitis in the 1970s. Our author team is also independent of commercial interests since none of the authors have any ties with the pharmaceutical industry. This is usually seen as a mechanism to achieve unbiased assessments of the evidence without overestimating benefits and underestimating harms [1].

Dr McGovern refers to the critique by Anna Lok (American Association for the Study of Liver Diseases (AASLD)) and William Powderly (Infectious Diseases Society of America (IDSA)) who submitted a comment shortly after Dr McGovern's and we address their concerns in a separate response below. Following independent assessment of the published review, we have made a number of amendments in collaboration with the office of Cochrane's Editor in Chief. These relate to clarifying the lack of RCT evidence for the validation of SVR as a surrogate outcome and reversing the decision to downgrade SVR for indirectness in the Summary of findings table.

Response References

Lundh A, Lexchin J, Mintzes B, Scholl JB, Bero L: Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2017, Art. No.: MR000033. DOI: 10.1002/14651858.MR000033.pub3.(2):MR000033.

Contributors: Janus C Jakobsen, Emil Eik Nielsen, Joshua Feinberg, Kiran Kumar Katakam, Goran Hauser, Goran Poropat, Snezana Djurisic, Milica Bjelakovic, Goran Bjelakovic, Sarah Louise Klingenberg, Jian Ping Liu, Ronald L Koretz, Christian Gluud.

Contributors

Comments made by: Barbara McGovern.

Comments addressed by: Janus C Jakobsen, Emil Eik Nielsen, Joshua Feinberg, Kiran Kumar Katakam, Goran Hauser, Goran Poropat, Snezana Djurisic, Milica Bjelakovic, Goran Bjelakovic, Sarah Louise Klingenberg, Jian Ping Liu, Ronald L Koretz, Christian Gluud.

Direct-acting antivirals for chronic hepatitis C, 31 July 2017

Summary

The following is a joint comment submitted by Anna S. Lok, President, American Association for the Study of Liver Diseases (AASLD) William G. Powderly, President, Infectious Disease Society of America (IDSA) on behalf of AASLD and IDSA. The comment has been endorsed by the American Gastroenterological Association (AGA), American College of Gastroenterology (ACG) and American Society for Gastrointestinal Endoscopy (ASGE).

Dear Editor,

We are writing to express our serious concerns regarding the recent Cochrane Group Review concluding that there is a lack of valid evidence supporting the benefit of direct acting antiviral (DAA) therapy for chronic infection with hepatitis C virus (HCV), and its supposition: "the possibility of potentially harming people with chronic hepatitis ought to be considered before treating people with hepatitis C with DAAs." Our review of this Cochrane publication suggests significant flaws in this analysis, yielding a misleading and a harmful conclusion.

The objective as stated is to assess the benefits and the harms of DAAs in people with chronic HCV. The selection criteria used only randomized clinical trials comparing DAA versus no intervention or placebo in patients with chronic HCV. Randomized trials in chronic HCV have only focused on the FDA recommended virologic endpoint of sustained virologic response (SVR), which is limited to a short follow-up period meant only to confirm permanent eradication of the virus from the blood stream. The Review's conclusion stating a lack of evidence that SVR impacts long term clinical outcomes (morbidity) and mortality ignores both fundamental mechanisms and mounting published literature supporting the clear clinical benefit of SVR obtained with DAAs.

First, experience from earlier HCV therapies (based on interferon), for which long term follow-up data are now available, clearly demonstrate numerous health benefits including a decrease in liver inflammation as reflected by improved aminotransferase levels and a reduction in the rate of progression of liver fibrosis as reflected in paired liver biopsy studies (Poynard, 2002). Of 3010 treatment-naive HCV-infected patients with pretreatment and posttreatment biopsies from four randomized trials of 10 different interferon-based regimens, 39 percent to 73 percent of patients who achieved an SVR had improvement in liver fibrosis and necrosis in liver biopsies separated by a mean of 20 months (Poynard, 2002). Cirrhosis resolved in half of the cases. Portal hypertension, splenomegaly and other clinical manifestations of advanced liver disease also improved. Among HCV-infected persons with advanced fibrosis, SVR is associated with a more than 70 percent reduction in the risk of hepatocellular carcinoma (HCC) and a 90 percent reduction in the risk of liver-related mortality and liver transplantation (Morgan, 2013); (van der Meer, 2012); (Veldt, 2007). It is precisely for these reasons that the FDA recommended SVR as the primary endpoint for all contemporary HCV trials. SVR is a validated surrogate for long-term benefits. Based on these data, there is every reason to expect that analogous clinical benefits will be observed with cure of HCV infection obtained via DAAs after a sufficient follow-up period.

Second, even early data from the DAA experience support clear improvements in clinical outcomes that can be measured in the short term. Cure of HCV infection immediately reduces symptoms and organ dysfunction from severe extrahepatic manifestations including cryoglobulinemic vasculitis, a complication affecting up to 10 percent of HCV-infected patients (Saadoun, 2017); (Sise, 2016). Historically, HCV-infected persons with non-Hodgkin lymphoma (NHL) and other B-cell lymphoproliferative disorders achieved complete or partial remission in up to 75 percent of cases following successful IFN-based therapy for HCV infection (Gisbert, 2005); (Takahashi, 2012); (Svoboda, 2005); (Mazzaro, 2002); (Hermine, 2002). Recent data show that DAA regimens produce similar remission rates in NHL and even higher rates of SVR (Arcaini, 2016). Perhaps the most striking evidence of direct clinical improvement comes from data demonstrating the success of DAAs in patients with decompensated liver disease for whom SVR was associated with improved MELD scores and albumin levels in the majority of patients with Child B and C cirrhosis (Charlton, 2015). Indeed, success in this group in many cases obviates the need for liver transplantation, meaning that more donor organs could become available to other patients on the waitlist (Belli, 2016). Thus, even without long term follow-up to prove a survival benefit, there are already clear indications of the clinical benefit of SVR offered by use of DAAs to reduce disease complications.

We are troubled by the implications of this review for the ongoing international efforts to halt the HCV epidemic, and to give patients back their futures. In the face of the National Academies of Science, Engineering, and Medicine statement that elimination of HCV is possible by 2030 with optimal implementation of high efficacy therapy, we believe that the Cochrane Review does a grave disservice to these efforts and to patients living with chronic HCV infection, a disease responsible for tens of thousands of deaths around the world each year. We stand behind our Associations' recommendations that all patients with HCV should be treated to prevent complications of this curable disease (www.hcvguidelines.org) and we will continue to fight for the global elimination of this viral infection. In light of the evidence that we have cited, we urge the Cochrane Review authors to retract or to revise their conclusions.

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Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?

Anna S. Lok's institution received research grants from AbbVie, BMS*, Gilead*, Idenix/Merck, Target Pharma*. Dr. Lok has served on the advisory panel of GlaxoSmithKline, Gilead, MYR, Tekmira (*Ongoing, all others have ended)

William G. Powderly has received research grants from Merck and has served as a consultant to Merck and Gilead.

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) are the sponsors of the Guidance and provide ongoing financial support. Grant support was sought and obtained from the Centers for Disease Control and Prevention (CDC) for the initial gathering and review of evidence related to hepatitis C screening and testing recommendations and interventions to implement HCV screening in clinical settings. No other financial support has been received for the HCV Guidance

AASLD and IDSA receive unrestricted educational grants from several companies for its CME and non-CME educational activities. Over the past 3 years grants and support have been received from the following companies for each society:

AASLD (as of June 22. 2017): AbbVie, Allergan, Astellas, Bristol Myers-Squibb, Diasorin, Gilead, The Henry M. and Lillian Stratton Basic Science Single Topic Conference Endowment, Lilly, Merck, National Genomics Institute, Salix and PSC Partners Seeking a Cure.

IDSA (During 2014-2016): AbbVie, Activas, Allergan, Astellas, Bristol Myers-Squibb, Cubist, Durata, Forest, Genocea, Gilead, GlaxoSmithKline, HEALIX, Merck, Pfizer, Salix, Sigma-Tau, Takeda, The Medicines Company, Theravance, and VIV.

Contributors: Anna S. Lok, President, American Association for the Study of Liver Diseases (AASLD); William G. Powderly, President, Infectious Disease Society of America (IDSA) on behalf of AASLD and IDSA.

Reply

We appreciate the fact that Lok and Powderly, submitting these comments on the behalf of several hepato-gastroenterological societies, have a continued interest in our systematic review on DAAs for people with chronic hepatitis C (1). We will respond below on a paragraph by paragraph basis. However, before doing so, we need to consider what we believe is the fundamental cause for our differences, namely the validity of using sustained disappearance of hepatitis C virus (HCV) RNA from the blood (the "sustained virological response" or SVR) as a surrogate outcome for more patient-centred clinical outcomes.

A surrogate outcome is typically a test that is associated with a better clinical outcome (morbidity or mortality) even though the surrogate itself may not intrinsically be beneficial to patients (2). Furthermore, the surrogate occurs earlier in the course of treatment, thus allowing for shorter trials to be conducted. However, in order to use a surrogate outcome as a substitute for a clinical outcome, it is necessary to validate it, to show that changes in the surrogate outcome are accompanied by similar changes in the clinical one (3). Because of biases such as confounding, validation has to be accomplished with randomised clinical trials (RCTs) that assess both surrogate and clinical outcomes. Ideally, this evidence should come from individual patient data. We consider the assertion that evidence from observational studies can validate a surrogate outcome to be unreliable: numerous studies both within and outside hepatology have shown that such judgments based on observational evidence are proved wrong (4-6).

The fact that the FDA and others have accepted the SVR as a surrogate for long term cure does not mean that this surrogate outcome has been validated (2). As noted, validation of a surrogate outcome requires RCTs that assess both clinical and surrogate outcomes, and show that the intervention changes both to the same degree and in the same direction (ideally also in the same patients) (3). Validation of SVR by these methods has never been successfully demonstrated. In fact, one effort in the interferon era to validate SVR in chronic hepatitis C failed to do so; while the recipients of interferon had more SVRs, they also had more morbidity and even appeared to have a higher all-cause mortality (7).

We agree with Lok and Powderly that the trials included in our systematic review were primarily designed to assess the effect of the intervention on the development of SVR. We have no evidence on long-term morbidity or mortality from the trials to support the view that DAAs improve these outcomes. Our uncertainty stems from the lack of evidence regarding whether or not DAA treatment (and we would point out that it is DAA treatment, not the SVR, that is the intervention) has any such effect. We did not claim that treatment had no clinical effect; rather, we claim that there was no evidence of such a clinical effect from randomised trials.

We would also note that if it is true that the benefit of the treatment begins at the time of achieving SVR, then it would be possible to see a clinical effect from adequately powered trials with relatively short-term follow-up. We seemed to have sufficient power to demonstrate that DAAs do not influence the risk of serious adverse events. Besides that, the main limitation of the evidence to date was the risk of bias and lack of power to see any effects on clinical outcomes.

We will comment on the fundamental mechanisms from the evidence cited by Lok and Powderly in our comments below. However, it is important to remember that, with the exception of conditions for which a bad outcome is absolutely predictable (e.g. the use of haemodialysis for permanent kidney failure; or the use of cardiopulmonary resuscitation for a cardiac arrest), only RCTs can demonstrate causal relationships between interventions and outcomes. Observational studies comparing different interventions (including placebo/no treatment) are confounded by at least one other factor, the reason why each intervention was provided.

Lok and Powderly cite a study by Poynard et al to support their contention that interferon-based therapies provide numerous health benefits. However, the reported benefits were changes in other surrogate outcomes (liver inflammation, necrosis, and progression of liver fibrosis). The Poynard study, while obtaining data from RCTs that compared different treatment regimens, reorganised the data such that the randomisation was lost. More importantly, no clinical outcomes were reported.

Lok and Powderly have not referred to a number of RCTs (including three large ones) that compared interferon with no treatment and reported clinical outcomes; these trials did not demonstrate any consistent meaningful clinical benefit (7). Even more concerning, the HALT-C trial reported an increase in all-cause mortality in the group receiving pegylated interferon in spite of the fact that the treated group achieved more SVRs than the untreated control group (8). That systematic review (7) also demonstrated that the interferon treatment did result in improvements in a number of these other surrogate markers (histological and biochemical markers of inflammation and fibrosis) in the absence of any consistent meaningful clinical benefits (7).

Lok and Powderly go on to claim that three studies showed an association between SVRs and reduced incidences of hepatocellular carcinoma and liver mortality. We note that the van der Meer paper was an update of the study by Veldt and the Morgan paper was a review that included an earlier abstract of the van der Meer study. Rather than show this as 'mounting evidence', data from the same patients are being used more than once to support their contention. All three observational studies used the same study design; all three studies compared treated patients who had achieved SVRs to treated patients who had not. While the data do show that those who achieve SVRs have better outcomes, that association cannot be attributed to treatment because both groups were treated. We do not believe that it is logical or correct to attribute benefit to treatment. As Flemming and DeMets concluded already in 1996, simply showing an association or a correlation between short-term measures and long-term clinical events does not validate a surrogate outcome (5). It has been recognized for decades that in comparison with those who do not achieve SVRs, those who do have underlying demographic characteristics that predispose them to develop less end-stage liver disease, even if they had been left untreated. Those achieving SVRs have less fibrosis, normal body weight, favourable ILB28 genotype, are female, have no coinfection with HIV or hepatitis B, etc. (9). It should also be remembered that only a minority of hepatitis C-infected individuals (15% or so in the inception cohort studies (9)) progress to end-stage liver disease after up to 4-5 decades of follow-up.

We must again note that the SVR cannot be considered a validated surrogate outcome, since validation cannot be established by observational studies.

The treatment of extra-hepatic processes (cryoglobulinaemia and lymphoproliferative diseases) that have been attributed to the hepatitis C virus is beyond the topic we covered in our systematic review, and we did not perform an in-depth search for trials that addressed the effect of DAA therapy in these situations. Thus, we cannot at this time comment on the effect of DAAs in these conditions in depth. The evidence cited by Lok and Powderly consists only of a case report, case series, and one systematic review of case series including some of the reports that were separately cited by Lok and Powderly. This again leads to the problem of relying on data from the same patients being used more than once. Lok and Powderly have not referred to any randomised clinical trials or systematic reviews of randomised clinical trials. Instead the studies cited showed that not all of the patients achieving SVRs had complete disease remissions and some of the patients received other non-antiviral treatments.

Lok and Powderly cite two studies that allegedly showed improvement in patients with decompensated cirrhosis who were treated with DAAs. The Charlton paper was a randomised clinical trial comparing two different durations of therapy in 337 patients who were separated

into 7 different groups by transplant status and various prognostic markers. The trial lasted for 6 to 9 months, during which time 13/373 died, 7/108 were transplanted, and 23% had serious adverse events, the majority of which were associated with hepatic decompensation. In the absence of a placebo control group, it is difficult to put any of this into perspective.

The Belli paper assessed 103 patients who were on a transplant list. The study was only reported after the data had been presented at a conference and this may represent a form of publication bias. More severe liver disease was an exclusion for treatment, resulting in the failure to treat 31 other (and sicker) patients, representing selection bias. During the course of the study (14 to 15 months), about 41 patients were transplanted and about 5 died. 21 of the remaining patients were delisted. The criterion for listing was a MELD score > 15 unless there were particular other circumstances; 17/21 who were delisted were among the 35 on the transplant list in spite of having a MELD score $\leq$ 15. Again, in the absence of a control group, it is difficult to understand how much, if any, benefit was achieved.

There were enough events in these populations that the value of treatment in such patients could be established by a treatment-no treatment RCT. It is curious that Lok and Powderly are not recommending such a trial.

Finally, Lok and Powderly believe that observational studies of DAA treatment with short-term follow up are all that is needed to demonstrate an improvement in survival. However, they also criticize the use of RCTs of DAA treatment with short-term follow-up to claim that we were not able to show such an effect.

Expectations of success in reducing the hepatitis C epidemic rest on the assumption that SVR equates to a cure. We challenge this assumption because some patients with SVR still have evidence of HCV-RNA in other cells in their bodies, and that relapse with genetically-identical viruses can occur years later (9). This confirms the concern that the virus is latently present elsewhere in the body and, most importantly, that, even after a SVR, patients can continue to have their liver disease progress (9).

Lok and Powderly reference the AASLD-IDSA guideline. We believe that this guideline contains incorrect statements, e.g. comparing two treated groups to make a case for using treatment, assigning a Class I, Level A rating to the goal of treatment claiming that such treatment reduces all-cause mortality and liver-related health adverse consequences when no evidence from RCTs showing such benefits exists. This guideline has already been criticised because of potential conflicts of interest (10). What we need are large randomised clinical trials that can assess the benefits and harms of DAAs on both a short-term and long-term basis. Such trials are increasingly warranted as there are not only indications that liver disease may progress in spite of SVR (9), but an unexpectedly high rate of tumour recurrence seems to coincide with SVR (11). Moreover, DAAs have also recently been suspected of causing unexpected adverse events; the US Food and Drug Administration has affixed a 'Boxed Warning' to certain DAAs because of concerns about reactivation of hepatitis B (12).

We clearly disagree with Lok and Powderly, and we consider the evidence that they rely on to justify the continuance of this otherwise unproven and expensive intervention to be poor. Better evidence is needed to enable us to be certain about the long-term effects of DAA therapy in hepatitis C.

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Comments addressed by: Janus C Jakobsen, Emil Eik Nielsen, Joshua Feinberg, Kiran Kumar Katakam, Goran Hauser, Goran Poropat, Snezana Djurisic, Milica Bjelakovic, Goran Bjelakovic, Sarah Louise Klingenberg, Jian Ping Liu, Ronald L Koretz, Christian Gluud.

WHAT'S NEW

Date	Event	Description
9 September 2017	Feedback has been incorporated	Replies to published feedback added.
8 September 2017	New citation required and conclusions have changed	Text revised following independent evaluation of the published review: 1. Validity of Sustained Virological Response (SVR) as a surrogate for cure described in terms of lack of randomised evidence in Background. 2. Downgrading for very serious indirectness for SVR in Summary of Findings tables has been reversed. 3. Revised conclusions clarify that there has been no validation of SVR as a surrogate for cure from randomised trials.

HISTORY

Protocol first published: Issue 4, 2016
Review first published: Issue 6, 2017

Date	Event	Description
9 June 2017	Amended	A short paragraph in the result section of the abstract (starts with 'Withdrawn or discontinued DAAs...') was found to be displaced, and now, in this review version, this paragraph appears last but one. This improves the clarity of reporting of results. In addition, the review title under Plain Language Summary is now provided.

CONTRIBUTIONS OF AUTHORS

JCJ wrote the first draft of the protocol. All remaining authors contributed with comments for revisions. All authors reviewed the final version of the protocol and approved its validity for publication.

Fifteen review authors (EN, JF, KF, KK, GH, GP, SD, KW, MB, GB, SK, JP, DN, RK, JCJ) independently and in pairs assessed all identified articles for inclusion and exclusion, ensuring that an article was assessed by at least two authors. If a trial was identified as relevant by one author, but not by another, the authors discussed the reasoning behind their decision. If they still disagreed JCJ or CG served as arbitrator. Twelve review authors (EN, JF, KF, KK, GH, GP, SD, KW, MB, GB, SK, DN) independently and in pairs extracted and validated data. We used data extraction forms that were designed for the purpose. The twelve authors discussed any disagreement concerning the extracted data. If the authors still disagreed, JCJ or CG served as arbitrator.

JCJ wrote the first draft of the review. All remaining authors contributed with comments for revisions. All authors reviewed the final version of the review and approved its validity for publication.

DECLARATIONS OF INTEREST

JCJ: none declared.
EN: none declared.
JF: none declared.
KK: none declared.
KF: none declared.
GH: none declared.
GP: none declared.
SD: none declared.
KW: none declared.
MB: none declared.
GB: none declared.
SK: none declared.
JP: none declared.
DN: none declared.
RK: none declared.
CG: none declared.

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- Dr Koretz receives ongoing support from Giissues Inc., a 501 (c) (3) non-profit organization that promotes the use and dissemination of evidence-based medicine. While no particular funds were used for this particular project, Giissues Inc. will support Dr Koretz's academic travel, society memberships, and other academic activities that have some relationship to the mission of the promulgation of evidence-based medicine. Giissues Inc. does not provide any salary support for Dr Koretz, USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Because of the unbalanced data, the large number of zero events, and the rare incidence of events in the control groups, we used reciprocal zero cell correction and fixed meta-analysis when analysing all-cause mortality and serious adverse events (STATA 14; www.stata.com) (Sweeting 2004; Deeks 2011). Otherwise, there are no differences between the planned methodology and the methodology used in this present review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [adverse effects] [*therapeutic use]; Cause of Death; Hepacivirus [drug effects]; Hepatitis C, Chronic [complications] [*drug therapy] [mortality]; Nucleic Acid Synthesis Inhibitors [adverse effects] [therapeutic use]; Placebos [therapeutic use]; Protease Inhibitors [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Safety-Based Drug Withdrawals; Simeprevir [adverse effects] [therapeutic use]

MeSH check words

Humans