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Direct-acting antivirals for chronic hepatitis C (Review)

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[Intervention Review]

Direct-acting antivirals for chronic hepatitis C

Janus C Jakobsen[1,2], Emil Eik Nielsen[3], Joshua Feinberg[3], Kiran Kumar Katakam[4], Kristina Fobian[3], Goran Hauser[5], Goran Poropat[5], Snezana Djurisic[4], Karl Heinz Weiss[6], Milica Bjelakovic[7], Goran Bjelakovic[8], Sarah Louise Klingenberg[1], Jian Ping Liu[9], Dimitrinka Nikolova[1], Ronald L Koretz[10], Christian Gluud[1]

[1]The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [2]Department of Cardiology, Holbaek Hospital, Holbaek, Denmark. [3]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [4]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [5]Department of Gastroenterology, Clinical Hospital Centre Rijeka, Rijeka, Croatia. [6]Internal Medicine IV: Gastroenterology, Infectious Diseases, Toxicology, Heidelberg University Hospital, Heidelberg, Germany. [7]Medical Faculty, University of Nis, Nis, Serbia. [8]Department of Internal Medicine, Medical Faculty, University of Nis, Nis, Serbia. [9]Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China. [10]Granada Hills, CA, USA

Contact address: Janus C Jakobsen, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, Copenhagen, Sjælland, DK-2100, Denmark. jcj@ctu.dk, janusjakobsen@mac.com.

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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) 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). However, it is still questionable if eradication of hepatitis C virus in the blood eliminates hepatitis C in the body, and improves survival and leads to fewer complications.

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.

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Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our primary outcomes were hepatitis C-related morbidity, serious adverse events, and 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 sustained virological response. We systematically assessed risks of bias, performed Trial Sequential Analysis, and followed an eight-step procedure to assess thresholds for statistical and clinical significance. The overall quality of the evidence was evaluated using GRADE.

Main results

We included a total of 138 trials randomising a total of 25,232 participants. The 138 trials assessed the effects of 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 withdrawn or discontinued DAAs. Trial participants were treatment-naive (95 trials), treatment-experienced (17 trials), or both treatment-naive and treatment-experienced (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.

Meta-analysis of the effects of all DAAs on the market or under development showed no evidence of a difference when assessing hepatitis C-related morbidity or all-cause mortality (OR 3.72, 95% CI 0.53 to 26.18, P = 0.19, I^2 = 0%, 2,996 participants, 11 trials, very low-quality evidence). As there were no data on hepatitis C-related morbidity and very few data on mortality (DAA 15/2377 (0.63%) versus control 1/617 (0.16%)), it was not possible to perform Trial Sequential Analysis on hepatitis C-related morbidity or all-cause mortality.

Meta-analysis of all DAAs on the market or under development showed no evidence of a difference when assessing serious adverse events (OR 0.93, 95% CI 0.75 to 1.15, P = 0.52, I^2 = 0%, 15,817 participants, 43 trials, very low-quality evidence). The Trial Sequential Analysis showed that the cumulative Z-score crossed the trial sequential boundary for futility, showing that there was sufficient information to rule out that DAAs compared with placebo reduced the relative risk of a serious adverse event by 20%. The only DAA that showed a significant difference on 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, then the meta-analysis result showed no evidence of a difference.

DAAs on the market or under development seemed to reduce the risk of no sustained virological response (RR 0.44, 95% CI 0.37 to 0.52, P < 0.00001, I^2 = 77%, 6886 participants, 32 trials, very low-quality evidence) and 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).

Withdrawn or discontinued DAAs had no evidence of a difference when assessing hepatitis C-related morbidity and 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). However, 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), and Trial Sequential Analysis confirmed this meta-analysis result.

Most of all outcome results were short-term results; therefore, we could neither confirm nor reject any long-term effects of DAAs. 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

Overall, DAAs on the market or under development do not seem to have any effects on risk of serious adverse events. 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 seemed to reduce the risk of no sustained virological response. The clinical relevance of the effects of DAAs on no sustained virological response is questionable, as it is a non-validated surrogate outcome. All trials and outcome results were at high risk of bias, so our results presumably overestimate benefit and underestimate harm. The quality of the evidence was very low.

PLAIN LANGUAGE SUMMARY

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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 interventions have been used for hepatitis C, but none of these interventions have proven effective on patient-centred outcomes. 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). However, it is questionable if an eradication of hepatitis C virus in the blood leads no hepatitis C in the body and improved survival and fewer complications. In this Cochrane Review, the authors assessed the evidence on the clinical effects of DAAs for hepatitis C.

Study characteristics

The authors included 351 publications of 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 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

DAAs do not seem to have any effects on the risk of hepatitis C-related morbidity or all-cause mortality. In fact, there were no data on hepatitis C-related morbidity and very few data on mortality (15 deaths/2377 direct-acting antiviral participants (0.63%) versus 1 death/617 control participants (0.16%) resulting in an odds ratio of 3.72, 95% CI 0.53 to 26.18, P = 0.19, I^2 = 0%, 2996 participants, 11 trials, very low-quality evidence). DAAs do not seem to have any effects on the risk of serious adverse events (376/13,574 (2.77%) direct-acting antiviral participants had one or more serious adverse events versus 125/2,243 (5.57%) control participants during the observation period resulting in an odds ratio of 0.93, 95% CI 0.75 to 1.15, P = 0.52, I^2 = 0%, 15,817 participants, 66 trials, very low-quality evidence). 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 confirm or reject if DAAs have clinically relevant effects on other clinically relevant outcomes. Our results confirm that DAAs seem to have an effect on the risk of no sustained virological response, but all of the trial results were at high risk of systematic error ('bias'), and the clinical relevance of results on virological response is questionable. The lack of valid evidence and the possibility of potentially harming people with chronic hepatitis ought to be considered before treating people with hepatitis C with DAAs.

Quality of the evidence

Due to several limitations, we assessed the quality of the evidence in this review as very 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. Third, most trials primarily focused and assessed the effects of DAAs on sustained virological response; however, it is questionable if sustained virological response has any clinical relevance to the person with chronic hepatitis C (see 'Background' in this Plain language summary).

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

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)	◯◯◯◯ Very 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 four levels because of serious risk of bias (two levels because of the very high risk of bias in the included trials Figure 1) and serious imprecision of the evidence (two levels because none of the TSA boundaries are crossed so the information size is too low).
[2]Downgraded three levels because of serious risk of bias (two levels because of the very high risk of bias in the included trials Figure 1) and serious indirectness (one level because 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 four levels because of serious risk of bias (two levels because of the very high risk of bias in the included trials Figure 1) and serious indirectness (two levels because no sustained virological response is a non-validated outcome; see Description of the condition and Agreements and disagreements with other studies or reviews).

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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 is 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 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). However, approximately 20% of infected people develop acute hepatitis (Koretz 2015) and in 80% of infected people 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, 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 defined as aviraemia 24 weeks after antiviral therapy (Ermis 2015)). It is important to appreciate that sustained virological response is a surrogate outcome that has never been validated (Garattini 2016; Gluud 2007; Koretz 2015). E-Serag 2016 have recently shown in a retrospective cohort study that the risk of hepatocellular carcinoma after obtaining sustained virological response remains relatively high at 0.33% per year (E-Serag 2016). Older age and presence of cirrhosis at the time of sustained virological response are associated with a high enough risk to warrant surveillance (E-Serag 2016). This result indicates that sustained virological response is not a 'cure' for HCV. 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).

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 in-

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hibitors (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. 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).

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). Sustained virological response is as-

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sociated with increased survival and fewer liver-related complications as fibrosis may become stable or reverse slowly over time (EASL 2015). However, as we have described in Description of the condition, it is questionable whether sustained virological response is a valid surrogate outcome. The clinical effects of DAAs are unclear and have rightfully 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.

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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

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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.

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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

We only included randomised clinical trials. For cross-over trials, we only included participants from the first treatment period in the trial. For trials with multiple experimental intervention arms we adequately divided the number of control participants so no control participant was counted more than once. 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-

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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 previously there has been 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.

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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).

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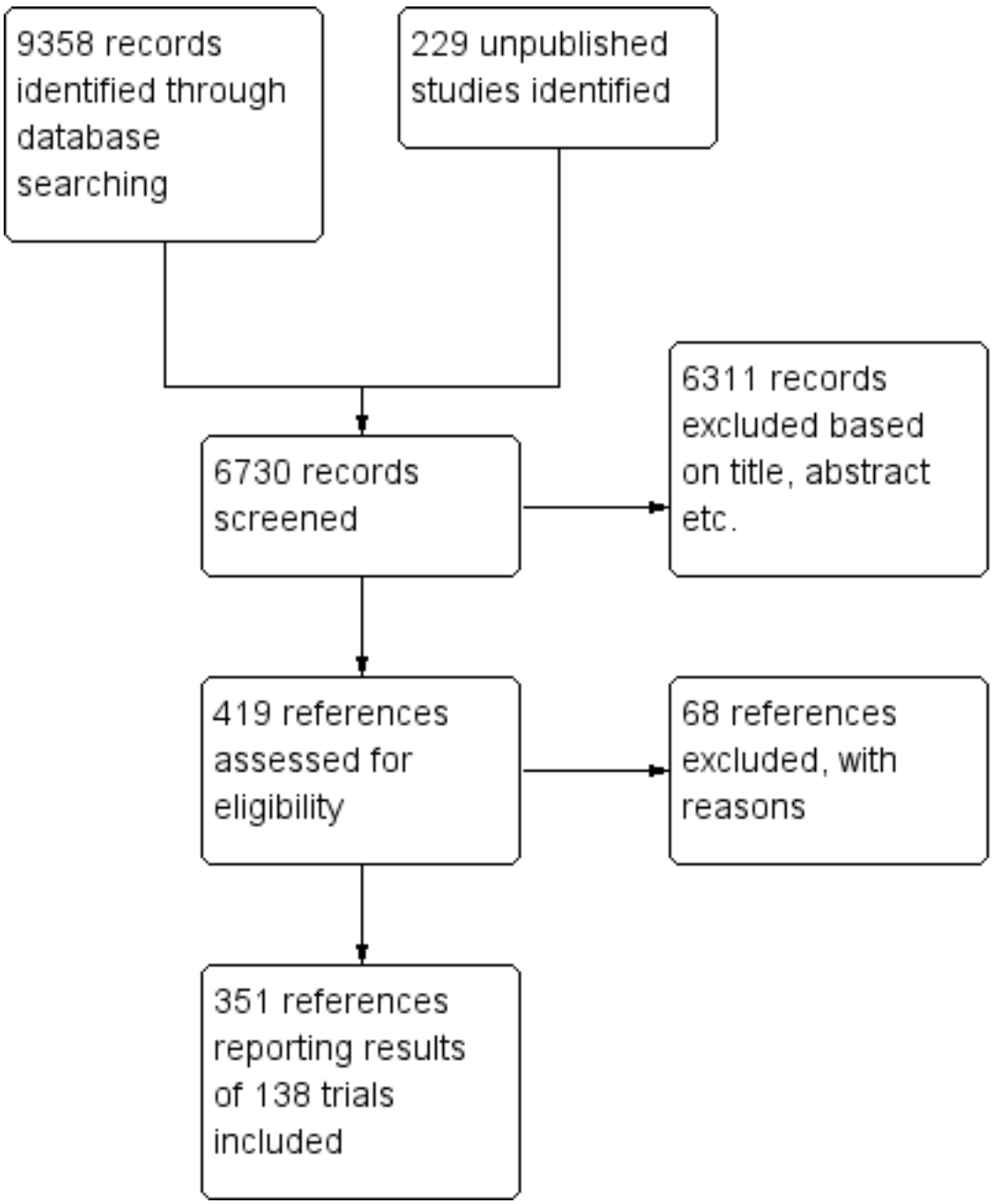
Figure 2. Study flow diagram



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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.

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

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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.

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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 standard results section, but the meta-analysis results can be found in the STATA forest plots. 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 forest 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).

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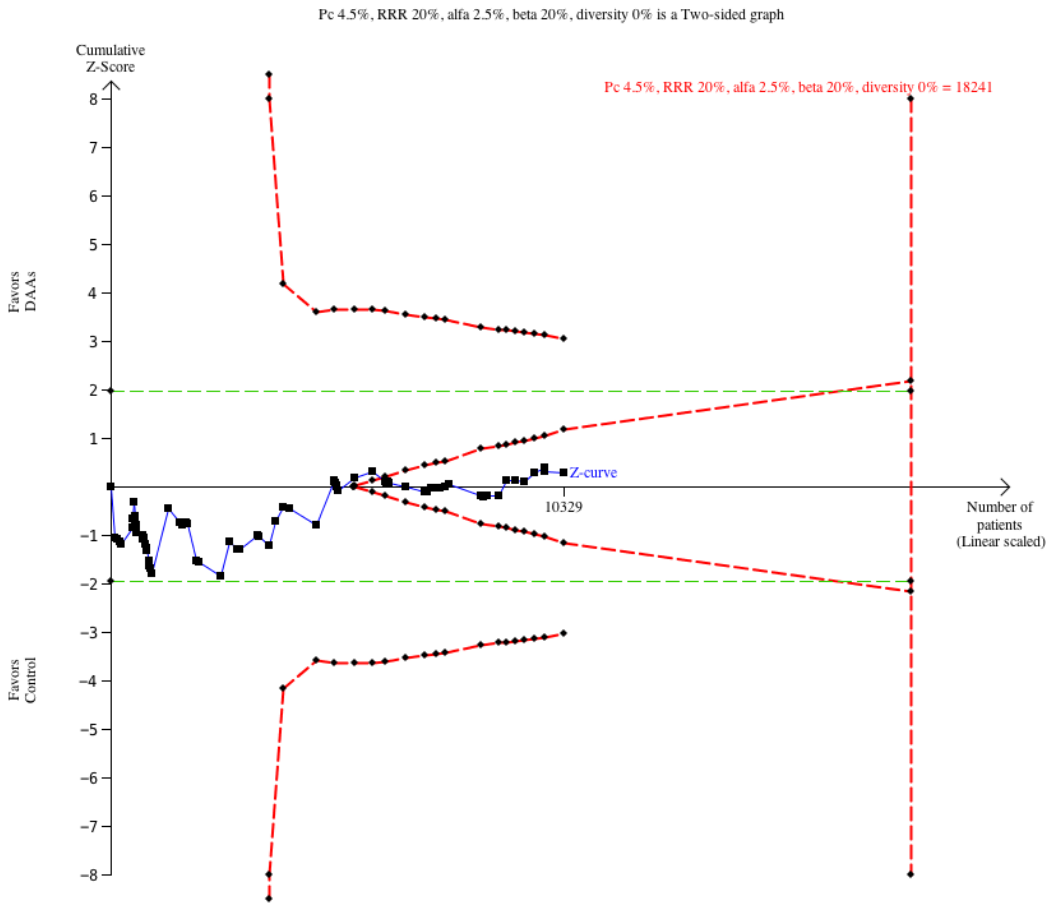
Figure 3. Trial Sequential Analysis of the effects of direct-acting antivirals on the market or under development versus placebo or no intervention on risk of serious adverse events. The analysis was based on a proportion in the control group (Pc) of 4.5%, a relative risk reduction (RRR) of 20%, and 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 bias 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-

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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).

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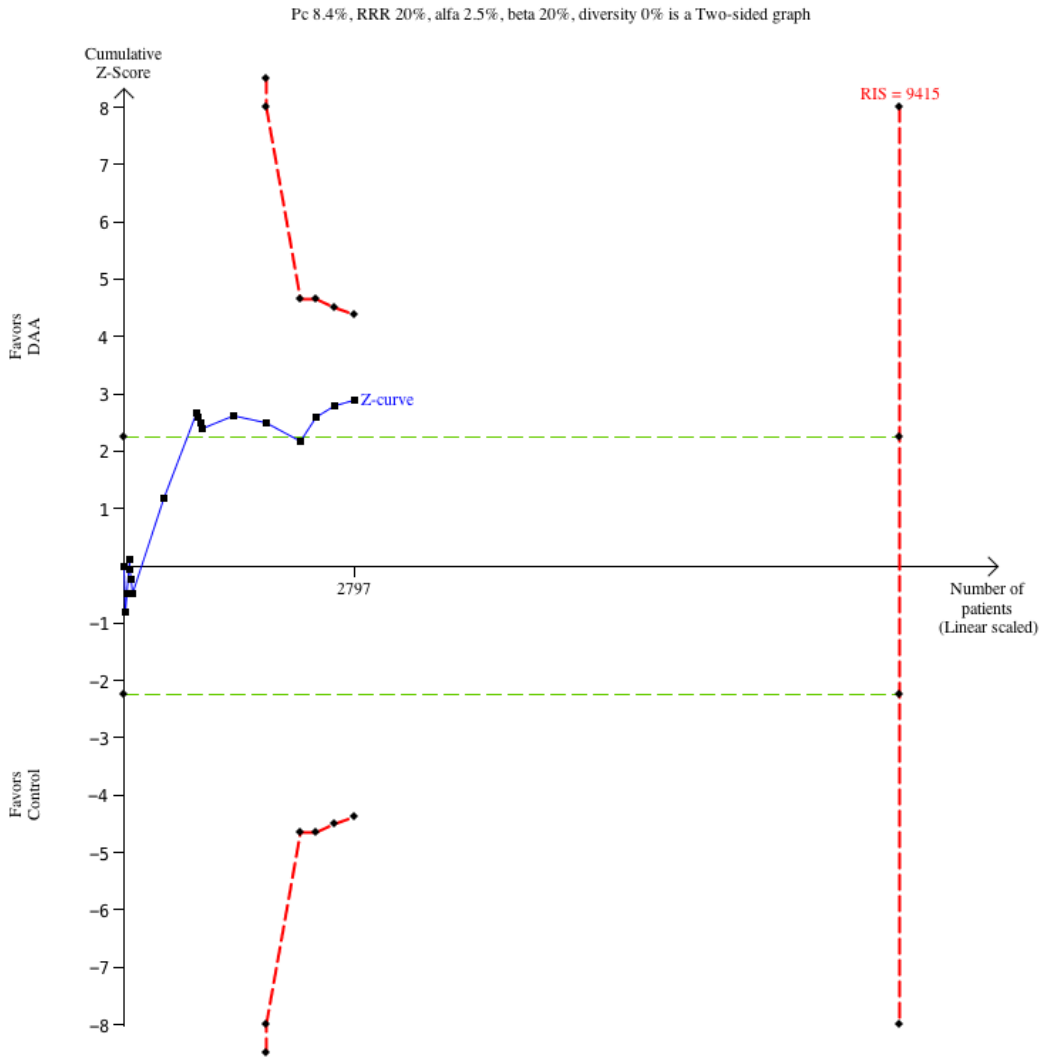
Figure 4. Trial Sequential Analysis of the effects of simeprevir versus placebo or no intervention on risk of serious adverse events. The analysis was based on a proportion in the control group (Pc) of 8.4%, a relative risk reduction (RRR) of 20%, and alfa of 2.5%, a beta of 20%, and a diversity of 0%.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



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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 1180/1692 (69.7%) in the DAA groups and a total of 915/5194 (17.6%) 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, very low-quality evidence; Analysis 3.1).

Heterogeneity

Visual inspection of the forest 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).

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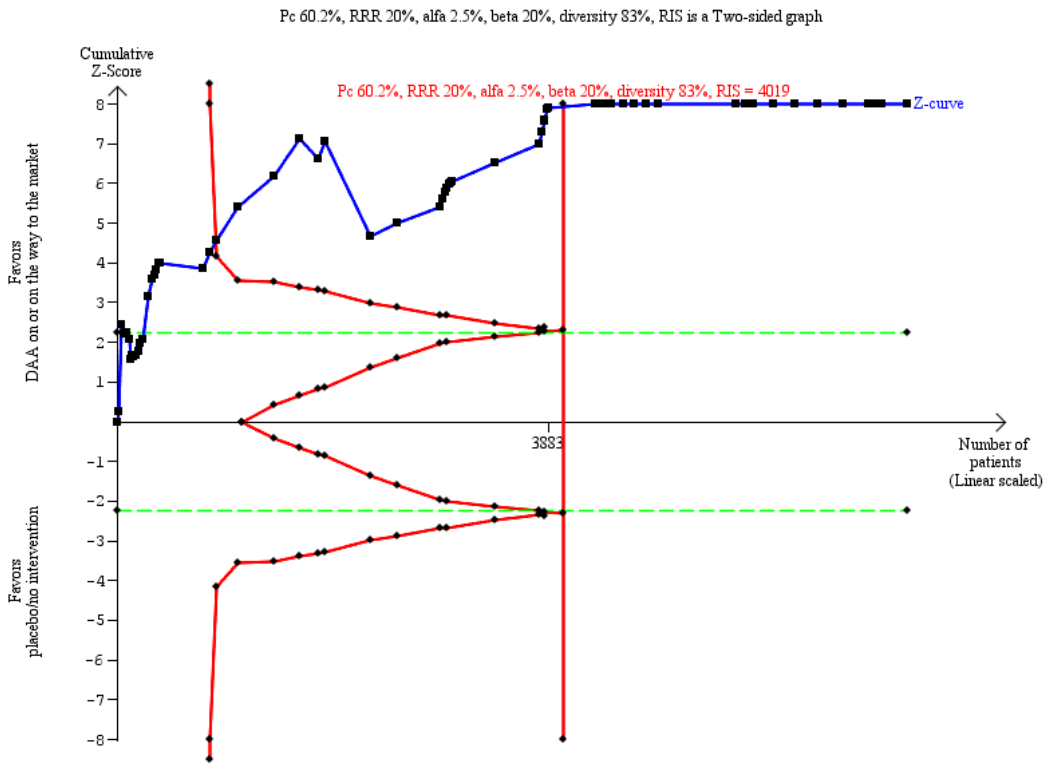
Figure 5. Trial Sequential Analysis of the effects of direct-acting antivirals on the market or under development versus placebo or no intervention on risk of no sustained virological response. The analysis was based on a proportion in the control group (Pc) of 60.2%, a RRR of 20%, and alfa of 2.5%, 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).

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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 a 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)

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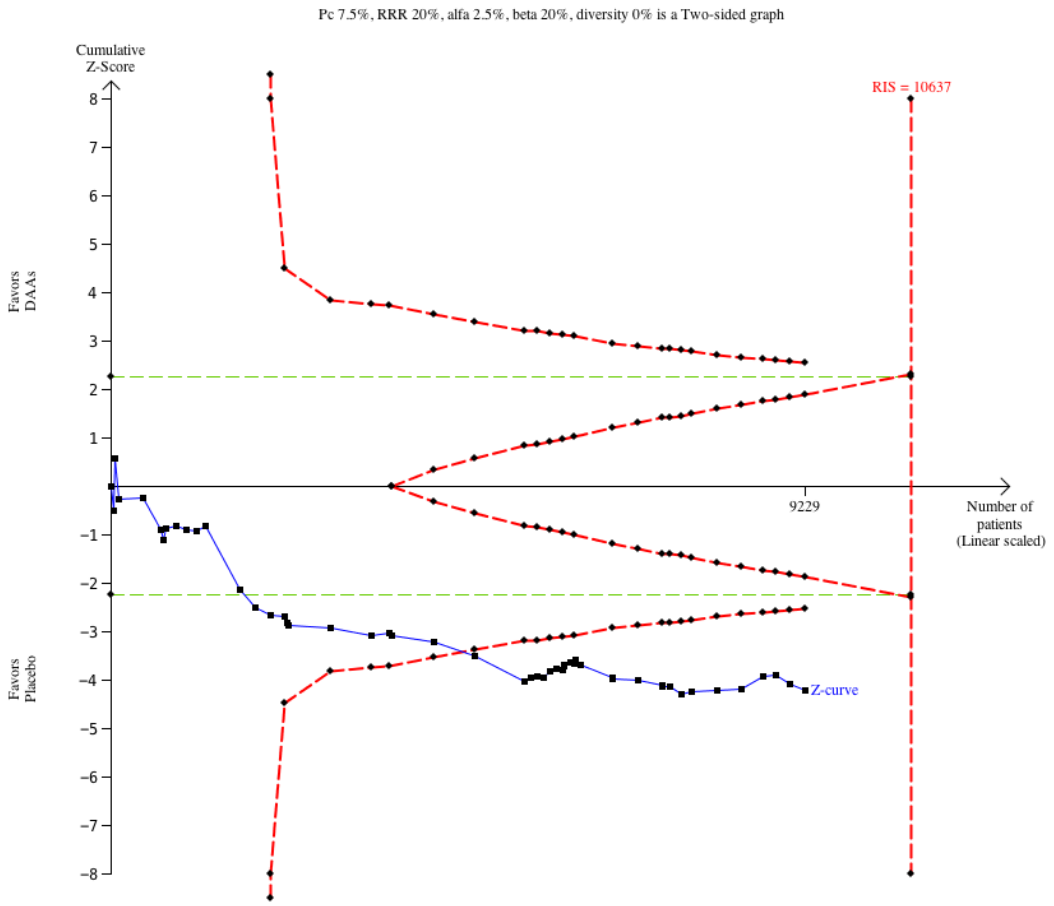
Additional analyses

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).

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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.

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ADDITIONAL SUMMARY OF FINDINGS [Explanation]

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)	◯◯◯◯ Very 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

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 four levels because of serious risk of bias (two levels because of the very high risk of bias in the included trials Figure 1) and serious imprecision of the evidence (two levels because none of the TSA boundaries are crossed so the information size is too low).

[2]Downgraded three levels because of serious risk of bias (two levels because of the very high risk of bias in the included trials Figure 1) and serious indirectness (one level because 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 four levels because of serious risk of bias (two levels because of the very high risk of bias in the included trials Figure 1) and serious indirectness (two levels because no sustained virological response is a non-validated outcome; see Description of the condition and Agreements and disagreements with other studies or reviews).

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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 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 beneficial effect when assessing risk of a serious adverse event. 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, which is a non-validated surrogate outcome (Gluud 2007). 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 as well as a high risk of publication bias, and the clinical relevance of the results on sustained virological response is questionable because it is a non-validated surrogate outcome. Our main results are summarised in Summary of findings for the main comparison. The quality of the evidence was 'very low' according to GRADE.

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 of the meta-analysis of the effects of DAAs on risk of no sustained virological response showed signs of asymmetry. This might indicate that we are missing data from smaller trials, presumably showing fewer or no beneficial effects of DAAs on risk of no sustained virological response. However, other types of bias might also cause the funnel plot asymmetry.

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 questionable.

Quality of the evidence

Heterogeneity

We assessed statistical heterogeneity as low in all of our results. Ths increases the validity of our reported results.

Risk of systematic error ('bias')

We found no trials or outcome results at low risk of bias, resulting in downgrading twice for the quality of evidence for all outcomes. See 'Risk of bias in included studies' for details. There is a high risk of our results showing an overestimation of benefit and underestimation of harm (Savović 2012a).

We found signs of asymmetry in the funnel plot of no sustained virological response. Hence, there is a suspicion of publication bias or other types of bias on this outcome result.

Risk of random error ('play of chance')

The 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 boundary for benefit was crossed in the Trial Sequential Analysis of no sustained virological response showing that, if risk of bias is disregarded, there is firm evidence that DAAs reduce the risk of no sustained virological response.

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GRADE

We have assessed the quality of the evidence for the results of each outcome using GRADE (Summary of findings for the main comparison). The GRADE assessments showed that the quality if the evidence was very low. 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.

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 trial results 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

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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. However, these reviews all primarily focused 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). Neither of the identified previous reviews systematically assessed the risks of bias or the risks of random errors. 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 is associated with improved clinical outcomes (Smith-Palmer 2015). However, the results of these observational studies should be interpreted with great 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; while the two subgroups had different prognoses, it is incorrect to attribute these different outcomes to treatment because they were all treated. The comparisons between those who achieved sustained virologic response and those never treated are confounded by the reason for the participants to have been, or not have been treated, and then further confounded by selection bias (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).

It should be appreciated that the focus of DAA treatment is the production of sustained virologic responses. However, this is a surrogate outcome that has not only never been validated, but failed validation in at least one scenario (Koretz 2013). In spite of this lack of validation, the sustained virologic response is, as referred to above, being called a 'cure'. This word is a misnomer, since we know that some patients who have sustained virologic response still can be shown to have HCV RNA in other cells (especially peripheral blood mononuclear cells), have the same (by RNA sequence analysis) HCV reappear in their serum months or years later, and go on to develop manifestations of end-stage liver disease (decompensated cirrhosis or hepatocellular carcinoma). These latter events are not rare; those who have stage 3 to 4 disease when the sustained virologic response is achieved develop end-stage liver disease at a rate of 1% to 2% per year (Koretz 2015; Koretz 2016)

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(see Description of the condition).

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, our results indicate that there seem to be no major clinical beneficial or harmful effects of DAAs in people with chronic HasseCV.

AUTHORS' CONCLUSIONS

Implications for practice

Direct-acting antivirals (DAAs), considered as one overall intervention, do not seem to have any effects on risk of serious adverse events in adults with chronic hepatitis C. There is insufficient evidence to judge if DAAs have beneficial or harmful effects on other clinical outcomes for chronic HCV. 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. DAAs may decrease the risk of no sustained virological response but the clinical implication of the results on this non-validated surrogate outcome is unclear. All the trials and all of the outcome results were at high risk of bias, so there is a great risk that out results overestimate benefits and underestimate harms. 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 non-validated surrogate outcome, that is, sustained virological response. This outcome has previously been shown to work as an invalid surrogate for clinical outcomes for the effects of IFNs or IFNs combined with ribavirin, as this may also be the case for DAAs;

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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Peer reviewers for the protocol: Thomas Baumert, France; Domenico Sansonno, Italy.

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Peer reviewers for the review: Thomas Baumert, France; Lauren A. Beste, US.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

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

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ADVANCE 2011a1 (*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	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
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

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ADVANCE 2011a2 (*Continued*)

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
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

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Anderson 2014a1 (*Continued*)

	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 **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

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Anderson 2014a1 (*Continued*)

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**
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

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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
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	

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Anderson 2014a4 (*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	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 2014a5

Methods	For characteristics see Anderson 2014a1	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Anderson 2014a5 (*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 2014a6

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

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Anderson 2014a6 (*Continued*)

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
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

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Anderson 2014a7 (*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 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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 5% of participants did not complete the study (19%), according to study protocol

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Anderson 2014a8 (*Continued*)

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

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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

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

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) 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

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Anonymous (PPI-461) 2011a3 (*Continued*)

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

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ASPIRE 2014 (*Continued*)

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)
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 $\geq$ 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 $\geq$ 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

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ATLAS 2013 (*Continued*)

	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
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

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	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) 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)

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	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 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.

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Bacon 2011a1 (*Continued*)

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 prespecified 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.

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Bacon 2011a2 (*Continued*)

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 **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

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Basu 2014a (*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	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
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

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Bavisotto 2007 (*Continued*)

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 **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

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Benhamou 2013a1 (*Continued*)

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
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**

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Benhamou 2013a2 (*Continued*)

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 **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

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Boehringer Ingelheim 2010a (*Continued*)

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 **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	

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Boehringer Ingelheim 2010b (*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	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 therapy. 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

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Bronowicki 2013a1 (*Continued*)

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	

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Bronowicki 2013a2 (*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)	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		
Bias	**Authors' judgement**	**Support for judgement**

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Bronowicki 2013a3 (*Continued*)

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

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Bronowicki 2014 (*Continued*)

	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
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

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Bronowicki 2014 (*Continued*)

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 **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).

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C-EDGE CO STAR 2015 (*Continued*)

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) All outcomes	Unclear risk	No description of dropouts after 12 weeks for the control group
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

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C-EDGE TN 2015 (*Continued*)

	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)
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

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Chandra 2006a (*Continued*)

	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
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

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COMMAND-1 2015a1 (*Continued*)

	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
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

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COMMAND-1 2015a1 (*Continued*)

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
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.

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COMMAND-1 2015a2 (*Continued*)

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
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

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CONCERTO-1 2015 (*Continued*)

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

Risk of bias

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

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Cooper 2009 (*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	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 **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

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Dauphine 2015a1 (*Continued*)

	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 $\geq$ 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

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Dauphine 2015a2

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
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	

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Dauphine 2015a3 (*Continued*)

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 % 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**

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Dauphine 2015a4 (*Continued*)

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 % 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.

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De Bruijne 2010a1 (*Continued*)

	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
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

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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
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

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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
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

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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

Risk of bias

Bias	Authors' judgement	Support for judgement

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Dore 2015a1 (*Continued*)

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
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants were only blinded during treatment period

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Dore 2015a2 (*Continued*)

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

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DRAGON 2014a1 (*Continued*)

	total). **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

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DRAGON 2014a2

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
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	

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DRAGON 2014a3 (*Continued*)

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 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

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DRAGON 2014a4 (*Continued*)

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

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	

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Erhardt 2009 (*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	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)	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 $\geq$ 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)

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Feld 2014 (*Continued*)

	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 **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

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Feld 2014 (*Continued*)

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) **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

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Feld 2015 (*Continued*)

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

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FISSION 2013 (*Continued*)

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
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 $\geq$ 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 $\geq$ 18 years, weight

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	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

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

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Flamm 2013 (*Continued*)

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 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

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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

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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	

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Forestier 2011a1 (*Continued*)

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) 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**

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Forestier 2011a2 (*Continued*)

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) 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 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

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	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
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

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Forestier 2011b (*Continued*)

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 $\geq$ 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 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:**

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	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

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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

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Foster 2011a1 (*Continued*)

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
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

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Foster 2011a2 (*Continued*)

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	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

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Foster 2015a1 (*Continued*)

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**
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	

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Foster 2015a2 (*Continued*)

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
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 pre-published 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:**

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	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 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**

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Fried 2013 (*Continued*)

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) All outcomes	Low risk	Withdrawals reported with reasons given. Treatment discontinuation rate 7.5%
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 (CDEB025A2210; 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

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	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. 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

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Fundamental 2014a1 (*Continued*)

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
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

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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
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

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Gane 2008 (*Continued*)

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%)
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,

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Gane 2010 (*Continued*)

	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 $\geq$ 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**
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"

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Gane 2010 (*Continued*)

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 immunosuppressive 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

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Gane 2011 (*Continued*)

	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

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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

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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 $\geq$ 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

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Gardner 2014a (*Continued*)

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 (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

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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
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

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Goldwater 2010 (*Continued*)

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**

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HALLMARK-DUAL 2014 (*Continued*)

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
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

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Han 2014 (*Continued*)

	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
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 preg-

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	nancy 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 $\geq$ 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 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 $\geq$ 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 $\geq$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 $\geq$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

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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. Number of participants with AEs. Number of participants with viral relapse. Maximum, minimum, and average plasma concentration of telaprevir
Notes	We 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

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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 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

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Hinrichsen 2004 (*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	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)
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

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	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 treatment 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

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Hoeben 2015a1 (*Continued*)

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**
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)

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Hoeben 2015a2 (*Continued*)

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.
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

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Hotho 2012 (*Continued*)

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

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

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Isakov 2016 (*Continued*)

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."
Other bias	Unclear risk	Unclear.

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
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	

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Izumi 2014a1 (*Continued*)

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
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Central randomisation centre

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Izumi 2014a2 (*Continued*)

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 $\leq$ 75 kg; 1200 mg/day orally in 2 divided doses for participants weighing > 75 kg
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

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Jacobson 2010 (*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	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: 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%)

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Jacobson 2014 (*Continued*)

	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 $\geq$ 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 $\geq$ 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

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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-ni ve 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

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	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 **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-re-

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JUMP-C 2013 (*Continued*)

		sponse 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)
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 $\geq$ 130 g/L (men), $\geq$ 120 g/L (women), neutrophil count $\geq$ 1.5 x 10^9/L, platelet count $\geq$ 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

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	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 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

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	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 $\leq$ 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

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

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Kwo 2010a1 (*Continued*)

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

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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	

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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
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

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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
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

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Kwo 2010a4 (*Continued*)

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
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

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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

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

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Lalezari 2012 (*Continued*)

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 significant 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

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Lalezari 2013 (*Continued*)

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. **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

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	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

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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)

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Larrey 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes stated in the protocol 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

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

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Lawitz 2008 (*Continued*)

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 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

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Lawitz 2009 (*Continued*)

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

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

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Lawitz 2010a (*Continued*)

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

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Lawitz 2010b (*Continued*)

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

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Lawitz 2010c (*Continued*)

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 **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

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Lawitz 2011a (*Continued*)

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

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Lawitz 2011b (*Continued*)

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

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Lawitz 2012a (*Continued*)

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
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

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Lawitz 2012b (*Continued*)

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
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 ≥ 1.25 × 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.

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Lawitz 2013a1 (*Continued*)

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) 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
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

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Lawitz 2013a2 (*Continued*)

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
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

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Lawitz 2013b (*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	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
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

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Lawitz 2013c (*Continued*)

	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
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

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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.
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

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Lawitz 2013d (*Continued*)

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
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

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Lawitz 2013e (*Continued*)

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.
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

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Lawitz 2013f (*Continued*)

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.
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

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Lawitz 2014a (*Continued*)

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
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

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Lawitz 2015 (*Continued*)

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 **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

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Liu 2015a (*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	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 **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

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Mallalieu 2014 (*Continued*)

	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

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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

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Manns 2011 (*Continued*)

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 (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 $\geq 4 \times 10^5$ 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 $\geq$ 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.

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Manns 2012a1 (*Continued*)

	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

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

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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
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	

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Manns 2012a3 (*Continued*)

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 2012a4

Methods	For characteristics see Manns 2012a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

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Manns 2012a4 (*Continued*)

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%)

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	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 $\geq$ 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 $\geq$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 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 $\geq$ 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

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Manns 2014a (*Continued*)

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 **Countries:** France, Moldova, Romania, USA
Interventions	**Experimental group:** oral ALS-2200 200 mg once daily for 7 days **Control group:** placebo for 7 days

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Marcellin 2013a (*Continued*)

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
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

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Marcellin 2013b (*Continued*)

	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 **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

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	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 interac-

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MATTERHORN 2015a1 (*Continued*)

		tive 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	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

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MATTERHORN 2015a2 (*Continued*)

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)

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	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 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

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McHutchison 2009 (*Continued*)

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
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 $\geq$ 1500 cells/mm^3, platelet count $\geq$ 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 $\geq$ 800,000 IU/mL, n(%): 106(92) Stage of fibrosis or cirrhosis, n(%): none or minimal: 26(23), portal fibrosis: 44(38),

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	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 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

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McHutchison 2010 (*Continued*)

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
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

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Mostafa 2015 (*Continued*)

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
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

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	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:** 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

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Muir 2014 (*Continued*)

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 **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

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Nelson 2011 (*Continued*)

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 **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

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	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
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

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Nelson 2012a1 (*Continued*)

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

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Nelson 2012a2 (*Continued*)

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 2012a3

Methods	For characteristics see Nelson 2012a1
Participants	
Interventions	
Outcomes	
Notes	
Risk of bias	

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Nelson 2012a3 (*Continued*)

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

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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)

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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

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Nelson 2012a5 (*Continued*)

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
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

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		< 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 **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).

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Nelson 2012b (*Continued*)

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/m² **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

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

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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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant did not complete the study until day 28

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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)

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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

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Nettles 2011a4

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 2011a5

Methods	For characteristics see Nettles 2011a1
Participants	
Interventions	

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Nettles 2011a5 (*Continued*)

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 2011a6

Methods	For characteristics see Nettles 2011a1
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

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Nettles 2011a6 (*Continued*)

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

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.

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Nishiguchi 2014a1 (*Continued*)

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
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

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Nishiguchi 2014a2 (*Continued*)

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) 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

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 $\geq$ 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

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	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 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

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OPERA 2011a1 (*Continued*)

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 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

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OPERA 2011a2 (*Continued*)

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

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OPERA 2011a3 (*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 2011a4

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

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OPERA 2011a4 (*Continued*)

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
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

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OPERA 2011a5 (*Continued*)

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

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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) All outcomes	Low risk	There were no dropouts

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Pasquinelli 2012a1 (*Continued*)

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)

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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

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Pearlman 2014 (*Continued*)

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
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;

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	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 $\geq$ 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

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

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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
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

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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. 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 $\geq$ 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)	Low risk	The participants and care providers were blinded up until week 8. Outcomes were only reported till week 8 and there-

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Pockros 2008a1 (*Continued*)

All outcomes		fore 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	
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

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Pockros 2008a2 (*Continued*)

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
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)

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Pockros 2008a3 (*Continued*)

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**
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

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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 $\geq 10^5$ 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

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

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Pol 2012 (*Continued*)

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

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

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Pol 2013 (*Continued*)

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**
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

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Poordad 2007 (*Continued*)

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) 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

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	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)
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	

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Poordad 2011a1 (*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 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	
Interventions	
Outcomes	

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Poordad 2011a2 (*Continued*)

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

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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 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."

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POSITRON 2013 (*Continued*)

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	

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Reddy 2007 (*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	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.

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Reesink 2006 (*Continued*)

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 child-

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	bearing 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
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

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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
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

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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 $\leq$ 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
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

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Rodriguez-Torres 2010 (*Continued*)

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 $\geq$ 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

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	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, ketoconazole, 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

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Rodriguez-Torres 2011a1 (*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	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)	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**

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Rodriguez-Torres 2011a2 (*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	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
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.

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Rodriguez-Torres 2013 (*Continued*)

	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**
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

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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 retreatment 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. 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

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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	
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

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Rodriguez-Torres 2014a2 (*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 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
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

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Rodriguez-Torres 2014a3 (*Continued*)

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
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

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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
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

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Rodriguez-Torres 2014b1 (*Continued*)

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

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Rodriguez-Torres 2014b2 (*Continued*)

		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
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.

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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

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.

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	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 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

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Sarrazin 2007 (*Continued*)

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 **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

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Schiff 2008 (*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 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 was above 5% dropouts and it was unclear how the trial handled missing data
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

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Silva 2013a1 (*Continued*)

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)
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

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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
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	

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Silva 2013a3 (*Continued*)

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

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Sims 2014 (*Continued*)

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
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

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	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
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.

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	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

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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

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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 consistent 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

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STARTverso-2 2014a1 (*Continued*)

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

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STARTverso-2 2014a2 (*Continued*)

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 **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

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STARTverso-3 2013a1 (*Continued*)

	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
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

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STARTverso-3 2013a2 (*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	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	
Interventions	
Outcomes	
Notes	

Risk of bias

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

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STARTverso-3 2013a3 (*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 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 CD4 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 antiretrovirals (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 CD4 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

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	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

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Sulkowski 2013a

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

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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
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	

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Sulkowski 2013b (*Continued*)

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) 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
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

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	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 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 $\geq$ 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)

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Sulkowski 2013c (*Continued*)

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

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

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	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. **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)

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Sullivan 2012 (*Continued*)

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.
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

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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. **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

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Tatum 2015a1 (*Continued*)

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**
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

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Tatum 2015a2 (*Continued*)

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 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

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

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

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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
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts

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Vince 2014 (*Continued*)

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 $\geq$ 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 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

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	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**
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. "

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Wedemeyer 2013 (*Continued*)

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

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Wilfret 2013 (*Continued*)

Notes	We emailed Wilfret and colleagues on 27 April 2016 for additional information but reply not received yet 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.

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Younossi 2015 (*Continued*)

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 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

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	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) 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**

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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. .."
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

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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) 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 $\geq$ 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

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Zeuzem 2014a (*Continued*)

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
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 pre-specified 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

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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
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

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(*Continued*)

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)
Mizokami 2015	Wrong intervention/control (compared RBV vs no RBV)
Molina 2015	Not randomised

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(*Continued*)

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

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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

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DATA AND ANALYSES

Comparison 1. DAA on or on the way to the market 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	71		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
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]
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]

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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]
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]
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]

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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]
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]

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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]
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]

Comparison 2. DAA on or on the way to the market versus placebo/no intervention

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]
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]

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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]
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]

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4.3 NS5B inhibitors (NPI)	8	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
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]
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]

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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
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
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]

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Comparison 3. DAA on or on the way to the market versus placebo/no intervention

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]
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]
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]

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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]
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]

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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]
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]
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]

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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]
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]

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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]

Comparison 5. All DAA versus placebo/no intervention/other medical intervention

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]

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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]
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]
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]

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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]
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]

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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]
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]
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]

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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]
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]

Comparison 6. All DAA versus placebo/no intervention/other medical intervention

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]

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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]
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]
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]

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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]
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]
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]

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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]
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]

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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
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]

Comparison 7. All DAA versus placebo/no intervention/other medical intervention

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]

Comparison 8. All DAA versus placebo/no intervention/other medical intervention

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]

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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]
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]

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

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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]

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]
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]

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