Common Drug Review
Clinical Review Report

October 2014

Drug	Sofosbuvir (Sovaldi)
Indication	Sofosbuvir is indicated for the treatment of chronic hepatitis C virus (CHC) infection in adult patients with compensated liver disease, including cirrhosis, as follows: • For the treatment of genotype 1 and genotype 4 CHC infection in combination with pegylated interferon and ribavirin (Peg-INF/RBV); • For the treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin.
Listing request	Gilead is requesting that sofosbuvir receive a positive listing recommendation for the treatment of patients with CHC, based on the following criteria: • treatment-naive patients with chronic hepatitis C virus (HCV) genotype 1 infection • Peg-INF/RBV-experienced patients with chronic HCV genotype 2 infection • Peg-INF/RBV-experienced patients with chronic HCV genotype 3 infection; and • genotype 2 and 3 CHC patients for whom interferon is medically contraindicated.
Manufacturer	Gilead Sciences Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with CDR Update — Issue 87, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
CHC	chronic hepatitis C
CI	confidence interval
CLDQ-HCV	Chronic Liver Disease Questionnaire — Hepatitis C Virus
DAA	direct-acting antiviral
DB	double-blind
FACIT-F	Functional Assessment of Chronic Illness Therapy — Fatigue
HBV	hepatitis B virus
HCV	hepatitis C virus
ITT	intention-to-treat
LLOQ	lower limit of quantification
NMA	network meta-analysis
Peg-INF/RBV	Pegylated plus ribavirin
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SVR	sustained virologic response
SVR12	sustained virologic response for 12 weeks
SF-36-MCS	Short-Form 36 — Mental Component Summary
SF-36-PCS	Short-Form 36 — Physical Component Summary
WDAE	withdrawal due to adverse event
WPAI-HepC	Work Productivity and Activity Impairment — Hepatitis C

EXECUTIVE SUMMARY

Introduction

Hepatitis C virus (HCV) is an RNA virus that infects approximately 242,000 Canadians, although it is believed there are a number of infected individuals who are unaware that they have HCV. Of those infected, approximately 25% clear infection spontaneously (range 15% to 45%) and the remainder develop chronic hepatitis C (CHC).[1-3] There are six genotypes, and although treatment strategy tends to differ depending on genotype, there is no clear evidence that genotype affects disease severity. Genotype 1 infections are the least treatment responsive to treatment with pegylated interferon plus ribavirin (Peg-INF/RBV) and account for most HCV infections in Canadians (55% to 65%).[4-6] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, according to a recent review.[7]

For patients with CHC genotype 1, standard therapy has been Peg-INF/RBV therapy, administered for 48 weeks.[8] Genotype 2 patients are typically treated with 24 weeks of Peg-INF/RBV, as are genotype 3 patients, although genotype 3 is less responsive than genotype 2 to this regimen.[9] Greater understanding of the HCV replication cycle has resulted in the development of direct-acting antiviral (DAA) drugs that target several types of non-structural proteins used to support viral replication. The first two new DAAs were protease inhibitors, telaprevir and boceprevir, and they were approved in combination with Peg-INF/RBV for treatment of CHC infection with genotype 1. Recently, two new DAAs were approved by Health Canada (simeprevir and sofosbuvir). Simeprevir is a protease inhibitor approved for treatment of genotype 1 CHC, while sofosbuvir employs a novel mechanism of action, targeting an HCV polymerase. Sofosbuvir is the only DAA to be approved by Health Canada for treatment of CHC with multiple genotypes as described below.

Indication under review
SOVALDI (sofosbuvir) is indicated for the treatment of chronic hepatitis C (CHC) virus infection in adult patients with compensated liver disease, including cirrhosis, as follows: • For the treatment of genotype 1 and genotype 4 CHC infection in combination with pegylated interferon plus ribavirin (Peg-INF/RBV); • For the treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin.
Listing criteria requested by sponsor
Gilead is requesting that sofosbuvir receive a positive listing recommendation for the treatment of patients with CHC, based on the following criteria: • Treatment-naive patients with chronic hepatitis C virus (HCV) genotype 1 infection; • Peg-INF/RBV-experienced patients with chronic HCV genotype 2 infection; • Peg-INF/RBV-experienced patients with chronic HCV genotype 3 infection; and • Genotype 2 and 3 CHC patients for whom interferon is medically contraindicated.

Objective: To perform a systematic review of the beneficial and harmful effects of sofosbuvir in combination with other agents for the treatment of adults with CHC infection (genotypes 1, 2, 3, or 4).

Results and Interpretation

Included Studies

Five studies were included in this systematic review. One single-arm study (NEUTRINO) included patients with genotypes 1, 4, 5, and 6, while the others (FISSION, FUSION, POSITRON, and VALENCE) included patients with genotypes 2 and 3. Although NEUTRINO enrolled patients with one of four different genotypes, as described above, sofosbuvir does not have a Health Canada–approved indication for treatment of CHC infection with genotypes 5 or 6. In NEUTRINO (N = 327) patients were treatment naive and mostly genotype 1 (89%) or genotype 4 (9%), and all were treated with sofosbuvir+ Peg-INF/RBV for a total of 12 weeks.

FISSION (N = 499) was an open-label non-inferiority randomized controlled trial (RCT) that compared 12 weeks of sofosbuvir+ribavirin to 24 weeks of Peg-INF/RBV in a treatment-naive population. FUSION (N = 201) was a double-blind RCT that compared 12 weeks of sofosbuvir+ribavirin to 16 weeks of sofosbuvir+ribavirin, in patients who had failed prior treatment with pegylated interferon (peginterferon), with or without ribavirin. POSITRON (N = 280) was a double-blind RCT that compared 12 weeks sofosbuvir+ribavirin to placebo, in a population of patients who were intolerant, unwilling, or ineligible for peginterferon therapy. Finally, VALENCE was initially designed as a double-blind RCT comparing 12 weeks of sofosbuvir+ribavirin to placebo in a mixed treatment-naive and -experienced patient population. After a protocol amendment during the study, the placebo group was halted and the duration of sofosbuvir+ribavirin was extended to 24 weeks for patients with genotype 3, but remained 12 weeks for patients with genotype 2.

The primary outcome of all studies was the proportion of patients with sustained virologic response at week 12 post-treatment (SVR12). The non-inferiority margin for the primary outcome in FISSION was –15%. A major limitation of the NEUTRINO study was the lack of a comparator group. The analysis in NEUTRINO was based on an external control, and there are significant methodological limitations to such an approach. FISSION, the only active comparator study, used an open-label design, which increases the risk of bias, particularly for patient-reported outcomes such as quality of life. Also, in FISSION there were more withdrawals in the Peg-INF/RBV group than with the sofosbuvir+ribavirin regimen, and this differential rate of withdrawal may also have introduced bias into both the efficacy and safety analyses. All studies conducted with patients with genotypes 2 and 3 were limited by analyses that did not have sufficient statistical power to test between-treatment differences within specific subgroups defined by genotype or presence of cirrhosis.

Patients were generally in their late 40s and early to mid-50s at baseline, and the majority were male. In all studies except FUSION, the proportion of patients with cirrhosis was approximately 20%, while in FUSION, 34% of patients had cirrhosis at baseline.

Efficacy

a) Genotypes 1 and 4

Evidence of efficacy for the Health Canada–approved regimen of sofosbuvir for treatment of CHC genotypes 1 and 4 comes from one single-arm non-comparative trial that was restricted to treatment-naive patients. In NEUTRINO, the overall proportion of patients achieving SVR12 (91%) was statistically significantly greater than 60%, the external control response derived from studies of boceprevir and telaprevir and adjusted for expected differences in the percentage of patients with cirrhosis, and accepting a 5% trade-off in efficacy for an expected improved safety profile and shorter duration of therapy for sofosbuvir. Despite the provided rationale for the use of 60% as an appropriate external

control, NEUTRINO was a single-arm study whose patient population had uncertain comparability with those enrolled in the trials used for the external control, and this limits the conclusions that can be drawn from it.

NEUTRINO provided SVR12 results for subgroups based on genotype and presence or absence of cirrhosis, but again this trial lacks a comparator group. The proportion of patients with SVR12 response was 92% in genotype 1a, 82% in genotype 1b, and 97% with genotype 4. Based on the total trial population, the proportion of SVR12 responders in patients with cirrhosis was 80%, and without cirrhosis was 93%.

The proportion of patients relapsing in NEUTRINO was 9%. NEUTRINO assessed the impact of treatment on quality of life using a generic quality of life instrument (Short-Form 36), a disease-specific instrument (Chronic Liver Disease Questionnaire — Hepatitis C Virus [CLDQ-HCV]), in addition to the Functional Assessment of Chronic Illness Therapy — Fatigue (FACIT-F) and the Work Productivity and Activity Impairment — Hepatitis C (WPAI-HepC) instruments. Both SF-36 — Physical Component Summary (SF-36-PCS) and SF-36 — Mental Component Summary (SF-36-MCS) were statistically reduced (worse) from baseline to end of therapy with a mean ± standard deviation (SD) change from baseline of –6.5 ± 9.8 and –6.9 ± 10.6, respectively. Changes in the CLDQ-HCV (–0.6 ± 1.0) and FACIT-F (–19.8 ± 25.1) were also statistically significantly decreased (worsened) from baseline to end of therapy. The WPAI-HepC reported a mean ±SD increase (worsening) from baseline to end of therapy in the percentage of overall impairment of 22.1% ± 31.6 for work, and 22.0% ± 31.3 for activity. However, the clinical importance of these changes is uncertain, and there is no comparator group.

b) Genotypes 2 and 3

In FISSION, treatment-naive patients treated with a combination of sofosbuvir+ribavirin for 12 weeks had similar proportions of SVR12 responders to those treated with 24 weeks of Peg-INF/RBV (67% in each group, between-group difference of 0.3% [95% confidence interval (CI), –7.5% to 8.0%]); thus, the criteria for non-inferiority were met, with a lower bound for the 95% CI of –7.5%, greater than the non-inferiority margin of –15%. Superiority of the sofosbuvir+ribavirin regimen was not demonstrated. The proportion of genotype 2 patients achieving SVR12 was 97% with sofosbuvir+ribavirin and 78% with Peg-INF/RBV, and in genotype 3 patients was 56% and 63%, respectively. In patients with cirrhosis, the proportion of patients achieving SVR12 was 47% with sofosbuvir+ribavirin and 38% with Peg-INF/RBV, and in patients who did not have cirrhosis, the proportions were 72% and 74%, respectively. These subgroup data must be interpreted with caution as the study was not powered to draw any conclusions from these data. The proportion of patients relapsing was 30% with sofosbuvir+ribavirin and 21% with Peg-INF/RBV, and this was a statistically significant difference by Common Drug Review (CDR) analysis (relative risk [95% CI] 1.40 [1.02 to 1.93]; $P = 0.04$). Mean ±SD changes from baseline to end of treatment for the SF-36-PCS and SF-36-MCS were statistically significantly worse in the Peg-INF/RBV group compared with the sofosbuvir+ribavirin group; –4.3 ± 9.3 versus 0.5 ± 8.7 and –8.1 ± 12.8 versus –3.7 ± 11.5, respectively. However, the analysis was conducted on only a fraction of the intention-to-treat population (~40% of patients), and these analyses should also be interpreted with caution due to the multiple statistical testing.

In FUSION, patients who had failed on previous interferon-based therapy, treated with a 16-week regimen of sofosbuvir+ribavirin, had a statistically higher proportion of SVR12 responders compared with the 12-week sofosbuvir+ribavirin regimen (73% versus 51%, difference in proportions: –22% [CI, –34% to –10%], $P < 0.001$). In the subgroups, the proportion of SVR12 responders in genotype 2 was 94% with the 16-week regimen and 86% with the 12-week regimen, and in genotype 3, SVR12 responses were 62%

and 31%, respectively. In patients with cirrhosis, the proportion of patients with SVR12 was 66% with the 16-week regimen and 31% with the 12-week regimen, and in patients without cirrhosis was 76% and 61%, respectively. These subgroup data must be interpreted with caution as the study was not powered to draw any conclusions from these data. The proportion of relapsers was 27% with the 16-week sofosbuvir+ribavirin regimen and 47% with the 12-week sofosbuvir+ribavirin regimen and this was a statistically significant difference by CDR analysis (relative risk [95% CI], 1.72 [1.16 to 2.53]; $P = 0.006$). There were no statistically significant between-treatment differences in any of SF-36-PCS or SF-36-MCS), FACIT-F, CLDQ-HCV, or WPAI-HepC, based on mean changes from baseline to end of treatment.

In POSITRON (patients ineligible or unwilling to receive, or intolerant of, pegylated interferon), patients treated with sofosbuvir+ribavirin had a significantly higher proportion of SVR12 responders than placebo-treated patients (78% versus 0%, difference in proportions of 77% [95% CI, 71% to 84%], $P < 0.001$) after 12 weeks of treatment. The proportion of genotype 2 patients achieving SVR12 was 93% and for genotype 3 patients, 61%. In patients with cirrhosis, the proportion of patients with SVR12 was 61% and in patients without cirrhosis, 81%. These subgroup data must be interpreted with caution as the study was not powered to draw any conclusions from these data. In POSITRON, 21% of patients treated with sofosbuvir+ribavirin relapsed, and no placebo-treated patients relapsed, given that no patients responded. There were no statistically significant between-treatment differences in the SF-36 (SF-36-PCS or SF-36-MCS) based on mean change from baseline to end of treatment.

In VALENCE, the proportion of patients with an SVR12 was 93% for genotype 2 patients treated for 12 weeks with sofosbuvir+ribavirin and 85% in genotype 3 patients treated for 24 weeks with sofosbuvir+ribavirin. In patients with cirrhosis, the proportion of SVR12 responders was 82% in genotype 2 patients treated for 12 weeks, and 68% for genotype 3 patients treated for 24 weeks with sofosbuvir+ribavirin. For patients without cirrhosis, SVR12 responses were 94% in genotype 2 patients and 91% in genotype 3. With respect to relapses, in genotype 2 patients, 7% treated with the 12-week sofosbuvir+ribavirin regimen relapsed, and 14% of genotype 3 patients treated with the 24-week sofosbuvir+ribavirin regimen relapsed.

Harms

The proportion of patients experiencing a serious adverse event ranged between 1% and 5% across all studies.

Study withdrawal due to adverse events ranged between 0% and 12% across groups in the included studies, although the Peg-INF/RBV group in FISSION was the only group for which withdrawal due to adverse events was more than 4%. In FISSION, 1% of sofosbuvir+ribavirin patients and 12% of Peg-INF/RBV patients withdrew due to an adverse event. Note that the Peg-INF/RBV group was treated for 24 weeks, while the sofosbuvir+ribavirin group was treated for 12 weeks in this study.

The most common adverse events in the sofosbuvir+ribavirin regimens were fatigue (range: 23% to 47%), headache (21% to 33%), nausea (13% to 31%), and insomnia (11% to 29%). These were also the most common adverse events in the sofosbuvir+ Peg-INF/RBV and Peg-INF/RBV groups in FISSION (fatigue: 36% and 55%; headache: 25% and 44%; nausea: 18% and 29%; insomnia: 12% and 29%, respectively) and in the sofosbuvir+ Peg-INF/RBV group in NEUTRINO (fatigue: 59%; headache: 36%; nausea: 34%; insomnia: 25%).

There was one sofosbuvir+ribavirin patient with neutropenia (grade 4) across all the studies, while in FISSION, 12% of Peg-INF/RBV patients experienced grade 3 neutropenia and 3% experienced grade 4

neutropenia. Similar results were seen with sofosbuvir+ Peg-INF/RBV in NEUTRINO (grade 3: 15%; grade 4: 5%). Anemia occurred with 8% of sofosbuvir+ribavirin patients and 12% of Peg-INF/RBV patients in FISSION. In POSITRON, 13% of sofosbuvir+ribavirin patients had anemia, and none in placebo.

There is a lack of direct evidence comparing efficacy and harms of sofosbuvir+ Peg-INF/RBV with other DAAs and Peg-INF/RBV combinations in the treatment of CHC genotype 1 infection. The manufacturer submitted a network meta-analysis (NMA) comparing the efficacy of sofosbuvir+ Peg-INF/RBV with boceprevir+ Peg-INF/RBV and telaprevir+ Peg-INF/RBV in treatment-naive CHC genotype 1–infected patients, based on the outcome of sustained virologic response (SVR). The analysis did not provide convincing evidence of between-treatment differences in efficacy for the included treatments, and the NMA did not include all treatments of interest (simeprevir+ Peg-INF/RBV was not included in the manufacturer's NMA).

Other Considerations

Treatment of CHC is a therapeutic area in rapid evolution, with a number of interferon- and ribavirin-free regimens moving toward regulatory approval. Several regimens that are expected to receive regulatory approval in the near future include sofosbuvir. The COSMOS study examined regimens that combine sofosbuvir with simeprevir (with or without ribavirin). Although the sample was small, genotype 1 patients who received sofosbuvir plus simeprevir had a 100% SVR12 (N = 16) after 24 weeks of therapy. With 12 weeks of therapy, the SVR12 was 93% (N = 14).[10] These patients were either previous null responders, or treatment naive, but all had advanced cirrhosis/fibrosis. The 2014 European Association for the Study of the Liver (EASL) guidelines list 12 weeks of sofosbuvir plus simeprevir as an option for genotype 1 patients, although it is option 5, with a B1 recommendation. The authors of the EASL guidelines note that there does not appear to be a major advantage in adding ribavirin, unless the patient is a prior non-responder or has evidence of cirrhosis.[11,12] The 2014 American Association for the Study of Liver Diseases guidelines recommend sofosbuvir plus simeprevir (with or without ribavirin) for genotype 1 patients ineligible for interferon (Class I, Level B).[13] This combination has not received regulatory approval by Health Canada, but has been submitted to the Food and Drug Administration (FDA), according to a recent press release.[14]

Pharmacoeconomic Summary

The manufacturer submitted a confidential price of [redacted] per day, which corresponds to a total cost per course of treatment of [redacted], [redacted], and [redacted] per 12, 16, and 24-week regimen, respectively.

The manufacturer submitted a cost-utility analysis with a lifetime horizon. In genotype 1 treatment-naive patients, sofosbuvir in combination with Peg-INF/RBV for 12 weeks was compared with telaprevir plus Peg-INF/RBV, boceprevir plus Peg-INF/RBV, and Peg-INF/RBV. In genotype 2 patients, sofosbuvir in combination with ribavirin (RBV) for 12 weeks was compared with Peg-INF/RBV or no treatment. In genotype 3 patients, sofosbuvir in combination with RBV for 16 weeks was compared with Peg-INF/RBV or no treatment. For efficacy data, in genotype 1 patients, without a comparator group in NEUTRINO, for the base-case analysis, SVR rates were chosen from the intervention group of the pivotal trials for telaprevir and boceprevir (SPRINT-2 and ADVANCE) and from IDEAL for Peg-INF/RBV (naive indirect treatment comparison). In genotype 2 and 3 patients, SVR rates with sofosbuvir were based on POSITRON (interferon ineligible, unwilling, or intolerant) and FUSION (prior-relapsers, non-responders).The cumulative incidence of complications over a patient's lifetime was forecasted using transition probabilities based on different sources. Difference in risk of adverse events (anemia, depression, rash) was obtained from different studies. During the natural disease progression phase, utility changes were dependent on whether the patient had achieved SVR or if disease was progressing.

Treatment-related utility decrements were applied to reflect the decrease in patients' quality of life while on antiviral therapy. Utility values were obtained from published literature. Drug costs were obtained from the Quebec Drug Formulary. Initial input for resource utilization pattern related to monitoring of patients was based on the UK standards, but was reviewed by a Canadian hepatologist and was costed generally using standard Ontario sources. The costs to manage adverse events were obtained from a retrospective study of the Quebec provincial drug reimbursement program (Régie de l'assurance maladie du Québec).

Results of Manufacturer's Analysis

- In genotype 1 treatment-naive patients, the incremental cost-utility ratio (ICUR) for sofosbuvir versus Peg-INF/RBV is $31,323 for non-cirrhotic and $1,197 for cirrhotic patients. ICURs for sofosbuvir versus boceprevir and telaprevir were less than $20,000 for non-cirrhotic patients, and sofosbuvir was dominant in cirrhotic patients.
- In genotype 2 and 3 patients ineligible, unwilling, or intolerant to interferon, the ICUR for sofosbuvir versus no treatment was less than $20,000 for genotype 2, and less than $60,000 for genotype 3. In genotype 2 patients who experienced a relapse or breakthrough to previous treatment with Peg-INF/RBV, the ICUR for sofosbuvir versus no treatment was less than $45,000 and less than $17,000 versus Peg-INF/RBV. In genotype 2 patients non-responders to Peg-INF/RBV, sofosbuvir versus no treatment or Peg-INF/RBV had an ICUR of less than $22,000 in non-cirrhotic patients, but was dominated in cirrhotic patients.
- In genotype 3 patients who experienced a relapse or breakthrough to previous treatment with Peg-INF/RBV, sofosbuvir versus no treatment had an ICUR of less than $45,000. The ICUR for sofosbuvir versus Peg-INF/RBV was $51,519 in non-cirrhotic patients and $5,777 in cirrhotic patients. In genotype 3 patients non-responders to Peg-INF/RBV, the ICUR of sofosbuvir versus no treatment or Peg-INF/RBV was $50,346 and $62,393, respectively, in non-cirrhotic patients. In cirrhotic patients, the ICUR for sofosbuvir versus no treatment or Peg-INF/RBV was below $24,000.

Interpretations and Key Limitations

CDR identified a number of limitations with the manufacturer's analyses that could affect the estimates of cost-effectiveness:

- The design of NEUTRINO and FUSION required use of historical controls and naive indirect comparisons, which generates uncertainty in the ICURs.
- Many of the comparisons were based on very small sample sizes and results in some subgroups were not consistent with overall findings from FUSION and POSITRON; e.g., cirrhotic patients presenting better SVR rates than non-cirrhotic patients.
- Potential longer duration of therapy with sofosbuvir in genotype 3 patients was not considered.

Common Drug Review Analyses

The following parameters were assessed in the reanalyses: use of Saskatchewan Drug Benefit drug costs; more conservative SVR estimates for sofosbuvir, based on the lower bounds of the 95% CI or credible intervals limits; utility increment assigned to patients who achieved SVR was reduced to 0.07; time horizon was shortened to 80 years of age instead of 100; a lower cost of anemia was used.

- In genotype 1 treatment-naive non-cirrhotic patients, the comparative cost-effectiveness of sofosbuvir with that of telaprevir, boceprevir, and Peg-INF/RBV is uncertain, due to lack of direct comparator in the NEUTRINO trial, and limitations and wide credible intervals in the manufacturer's NMA. Using SVR estimates from the NMA, the ICUR for sofosbuvir versus Peg-INF/RBV, telaprevir, and boceprevir was $50,266 per quality-adjusted life-year (QALY), $11,531 per QALY, and $14,030 per QALY, respectively. Using conservative SVR estimates, the ICUR for sofosbuvir versus

Peg-INF/RBV was $135,391, and sofosbuvir was dominated by telaprevir and boceprevir. In cirrhotic patients, using conservative SVR estimates, sofosbuvir had an ICUR of $7,119 versus Peg-INF/RBV and $3,237 versus boceprevir, but was dominated by telaprevir.

- In genotype 2 patients ineligible to receive Peg-INF/RBV, ICURs for sofosbuvir versus no treatment remained attractive, in both non-cirrhotic and cirrhotic patients ($28,983 and $3,268 per QALY, respectively). In genotype 2 patients with prior relapse or breakthrough, sofosbuvir was generally cost-effective versus no treatment and versus Peg-INF/RBV (ICURs ranging from $23,944 to $31,487 per QALY), except versus Peg-INF/RBV in cirrhotic patients ($62,162 per QALY). In genotype 2 prior non-responders, the ICUR for sofosbuvir versus no treatment or Peg-INF/RBV was less attractive in non-cirrhotic patients, ranging from $61,564 to $136,936, and sofosbuvir was dominated by Peg-INF/RBV and no treatment in cirrhotic patients.
- In genotype 3 patients ineligible to receive Peg-INF/RBV, ICURs for sofosbuvir versus no treatment were above $75,000 in both non-cirrhotic and cirrhotic patients. In genotype 3 patients with prior relapse or breakthrough, sofosbuvir was not cost-effective (either dominated or ICURs > $150,000) versus no treatment and versus Peg-INF/RBV in non-cirrhotic patients, but ICURs were less than $31,000 in cirrhotic patients. In prior non-responders, compared with no treatment and Peg-INF/RBV, sofosbuvir was either dominated, or had ICURs above $150,000.

The ICURs of sofosbuvir versus appropriate comparators varied widely across genotypes and various subgroups. Analyses in genotype 1 patients were limited by lack of direct comparative data. Most of the analyses in genotype 2 and genotype 3 patients were limited by the small sample size of the clinical trials used to inform efficacy inputs. Based on CDR reanalyses, sofosbuvir is likely cost-effective in the following subgroups: genotype 1 treatment-naive cirrhotic patients (compared with boceprevir and Peg-INF/RBV, but analyses were based on very small subgroups, and on a naive indirect treatment comparison); genotype 2 Peg-INF/RBV–ineligible and prior-relapsers or breakthrough (except cirrhotic patients) compared with no treatment and Peg-INF/RBV; genotype 3 prior-relapsers or breakthrough with cirrhosis, compared with no treatment and Peg-INF/RBV.

Conclusions

There were four RCTs included in this review that enrolled patients with genotypes 2 or 3 (FISSION, FUSION, POSITRON, and VALENCE), but only one single-arm study (NEUTRINO) that included patients with genotypes 1 or 4. The genotype 2/3 studies featured a variety of populations and interventions, and with respect to SVR12 responses, the combination of 12 weeks of sofosbuvir+ribavirin demonstrated non-inferiority to 24 weeks of Peg-INF/RBV in a treatment-naive population (FISSION), and superiority to placebo in a population that was ineligible for, intolerant to, or unwilling to take pegylated interferon (POSITRON). Subgroup data from FUSION and findings from the descriptive VALENCE study suggest that genotype 3 patients may benefit from a longer duration of sofosbuvir+ribavirin (up to 24 weeks), compared with genotype 2 patients (12 weeks); however, due to design limitations, these findings are hypothesis-generating only. The shorter and potentially more tolerable sofosbuvir+ribavirin regimen might be expected to provide relatively better quality of life compared with Peg-INF/RBV, but there was no evidence of this from the included studies, in part due to a considerable amount of missing data for this outcome that rendered questionable results.

NEUTRINO lacked a control group, but sofosbuvir+ Peg-INF/RBV was demonstrated to be superior, in terms of SVR, to an external control of 60% in a treatment-naive primarily genotype 1 and 4 population. CDR identified no studies of sofosbuvir in treatment-experienced CHC genotype 1 patients that met the criteria for inclusion in this systematic review.

Across all studies, there were no novel safety or tolerability issues that could be attributed to the addition of sofosbuvir to either ribavirin or Peg-INF/RBV. When compared with Peg-INF/RBV, sofosbuvir+ribavirin appeared to be more tolerable, as measured by withdrawals due to adverse events.

TABLE 1: SUMMARY OF RESULTS IN STUDIES OF GENOTYPES 1 AND 4

Outcome	NEUTRINO
	SOF12+Peg-INF/RBV12 N = 327
SVR12	
Patients, n/N (%)	296/327 (91)
Relapse	
n, N (%)	28/326 (9)
Mortality	
Deaths, N	0
HRQoL: SF-36-PCS	
Mean (SD) baseline	49.5 (10.0) N = 315
Mean (SD) change	–6.5 (9.8) N = 298, *P* < 0.001[a]
HRQoL: SF-36-MCS	
Mean (SD) baseline	50.6 (10.4) N = 315
Mean (SD) change	–6.9 (10.6) N = 298, *P* < 0.001[a]
Withdrawals	
Total, N (%)	35 (11)
Serious adverse events	
n, N (%)	4 (1)
WDAEs	
n, N (%)	5 (2)
Notable harms(s)	
Fatigue	194 (59)
Headache	118 (36)
Nausea	112 (34)
↓Neutrophils — grade 3	49 (15)
Grade 4	17 (5)

HRQoL = health-related quality of life; SF-36-MCS = Short-Form 36 — Mental Component Summary; SF-36-PCS = Short-Form 36 — Physical Component Summary; Peg-INF/RBV = pegylated interferon + ribavirin; SD = standard deviation; SF-36 = Short-Form 36; SOF12+Peg-INF/RBV12 = 12 weeks sofosbuvir + 12 weeks Peg-INF/RBV; SVR12 = sustained virologic response, 12 weeks; WDAE = withdrawals due to adverse event.
[a]*P* value based on Wilcoxon signed-rank test.
Source: Clinical Study Report for NEUTRINO.[15]

TABLE 2: SUMMARY OF RESULTS FOR GENOTYPES 2 AND 3

Outcome	FISSION		POSITRON		FUSION		VALENCE			
	SOF12RBV12 N = 256	Peg-INF/RBV24 N = 243	SOF12RBV12 N = 207	PLAC12 N = 71	SOF12RBV12 N = 103	SOF16RBV16 N = 98	SOF12RBV12 G2	SOF12RBV12 G3	SOF24RBV24 G3	PLAC12
SVR12										
n, N (%)	170/253 (67)	162/243 (67)	161/207(78)	0/71 (0)	51/100 (51)	69/95(73)	68/73(93)	3/11 (27)	213/250(85)	NR [a]
Difference in proportions (95% CI), *P* value	0.3% (–7.5% to 8.0%), *P* = 0.94 [b]		77% (71%, 84%), *P* < 0.001 [b]		–22% (–34% to 10%), *P* < 0.001 [a]		NA			
Relapse										
n, N (%)	74/249 (30)	46/217 (21)	42/205 (21)	0/0	47/100 (47)	26/95 (27)	5/73 (7)	6/11 (55)	34/249 (14)	NR [a]
RR (95% CI), *P* value	1.40 (1.02 to 1.93), *P* = 0.04 [c]		Not estimable		1.72 (1.16 to 2.53), *P* = 0.006 [c]		NA			
Mortality										
n	1	0	0	0	0	0	0	0	0	0
HRQoL: SF-36-PCS										
Mean (SD) baseline	47.3 (9.9) N = 98	49.0 (10.3) N = 97	47.0 (9.1) N = 145	44.8 (10.3) N = 51	47.7 (10.0) N = 98	47.2 (9.7) N = 94	NR	NR	NR	NR
Mean (SD) change to EOT	0.5 (8.7) N = 81	–4.3 (9.3) N = 68	–1.8 (7.7) N = 132	–0.5 (6.7) N = 48	–2.2 (7.5) N = 97	0.0 (7.0) N = 85	NR	NR	NR	NR
P value	*P* < 0.001 [d]		*P* = 0.57 [d]		*P* = 0.10 [d]					
HRQoL: SF-36-MCS										
Mean (SD) baseline	49.5 (11.2) N = 98	49.0 (10.6) N = 97	47.4 (11.3) N = 145	44.7 (13.0) N = 51	48.3 (12.0) N = 98	50.3 (10.3) N = 94	NR	NR	NR	NR
Mean (SD) change to EOT	–3.7 (11.5) N = 81	–8.1 (12.8) N = 68	–5.7 (12.3) N = 132	–2.1 (9.2) N = 48	–4.7 (11.6) N = 97	–3.5 (9.9) N = 85	NR	NR	NR	NR
P value	*P* = 0.012 [d]		*P* = 0.12 [d]		*P* = 0.27 [d]					
Withdrawals										
Total, N (%)	32 (13)	67 (28)	53 (26)	71 (100)	52 (51)	29 (30)	NR	NR		NR

Outcome	FISSION		POSITRON		FUSION		VALENCE			
	SOF12RBV12 N = 256	Peg-INF/RBV24 N = 243	SOF12RBV12 N = 207	PLAC12 N = 71	SOF12RBV12 N = 103	SOF16RBV16 N = 98	SOF12RBV12 G2	SOF12RBV12 G3	SOF24RBV24 G3	PLAC12
Serious adverse events										
n, N (%)	7 (3)	3 (1)	11 (5)	2 (3)	5 (5)	3 (3)	0	10 (4)	2 (2)	
WDAEs										
n, N (%)	3 (1)	29 (12)	5 (2)	3 (4)	1 (1)	0	1 (1)	1 (< 1)	1 (1)	
Notable harms(s)										
fatigue	92 (36)	134 (55)	91 (44)	17 (24)	46 (45)	46 (47)	19 (23)	75 (30)	16 (19)	
headache	64 (25)	108 (44)	43 (21)	14 (20)	26 (25)	32 (33)	24 (29)	74 (30)	23 (27)	
nausea	46 (18)	70 (29)	46 (22)	13 (18)	22 (21)	20 (20)	26 (31)	32 (13)	9 (11)	
↓Neutrophils — gr 3	0	30 (12)	0	1 (1)	0	0	1 (1)	0	1 (1)	
gr 4	0	6 (3)	0	0	1 (1)	0	0	0	0	

CI = confidence interval; EOT = end of therapy; G2 = genotype 2; G3 = genotype 3; HRQoL = health-related quality of life; SF-36-MCS = Short-Form 36 — Mental Component Summary; NR = not reported; PLAC12 = 12 weeks placebo; SF-36-PCS = Short-Form 36 — Physical Component Summary; Peg-INF/RBV12 = 12 weeks pegylated interferon+ribavirin; SD = standard deviation; SOF12RBV12 = 12 weeks sofosbuvir + 12 weeks ribavirin; SOF16RBV16 = 16 weeks sofosbuvir + 16 weeks ribavirin; SOF24RBV24 = 24 weeks sofosbuvir + 24 weeks ribavirin; RR = relative risk; WDAE = withdrawals due to adverse event.

[a]The placebo group of VALENCE was halted early, but the manufacturer notes that there were no viral responses in the placebo group at any time point.

[b]Difference in proportions between-treatment groups and associated 95% CI are calculated based on stratum-adjusted Mantel–Haenszel proportions.

[c]*P* value based on calculation of relative risk, performed by the Common Drug Review.

[d]*P* value based on Wilcoxon signed-rank test.

Source: Clinical Study Reports for FISSION,[16] VALENCE,[17] FUSION,[18] POSITRON,[19] and Zeuzem 2014 (VALENCE).[20]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hepatitis C infection is caused by an enveloped, single-stranded linear RNA virus of the Flaviviridae family. It is estimated that 0.8% or 242,000 Canadians have chronic hepatitis C virus (HCV) infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[21] In 2009, 11,357 cases of HCV were reported, mostly due to injection drug use.[22] There are six major HCV genotypes. While the HCV genotype strongly correlates with treatment response, there is no clear correlation between the infecting genotype and disease severity or the rate of disease progression. Genotype 1 infections are the least treatment responsive and account for most HCV infections in Canadians (55% to 65%).[4-6] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, according to a recent review.[7]

Of those infected, approximately 25% clear infection spontaneously (range 15% to 45%) and the remainder develop chronic infection.[1-3] Of those with chronic infection, 15% to 25% will develop progressive liver disease, end-stage liver disease, or hepatocellular carcinoma, or will require liver transplant.[23,24] Male gender, ethanol use, HIV coinfection, obesity, and increasing age are associated with an increased risk of liver disease progression. While incident cases of HCV in North America and Canada[25,26] continue to decline, it is expected that liver-related morbidity and mortality will continue to increase over the coming decades, as those who are already infected age.[21,27]

1.2 Standards of Therapy

Prior to 2011, pegylated interferon (peginterferon) plus ribavirin (Peg-INF/RBV) was the gold standard of therapy to inhibit viral replication in patients with chronic hepatitis C (CHC). Approximately half of patients with genotype 1 CHC, the most prevalent type of CHC in Canada, could expect to achieve sustained virologic response (SVR) with Peg-INF/RBV therapy. For patients with genotype I CHC, standard therapy has been Peg-INF/RBV therapy, administered for 48 weeks.[8] Genotype 2 patients are typically treated with 24 weeks of Peg-INF/RBV, as are genotype 3 patients, although genotype 3 is less responsive than genotype 2 to this regimen.[9] Greater understanding of the hepatitis C viral replication cycle has resulted in the development of direct-acting antiviral (DAAs) drugs that target several types of non-structural proteins used to support viral replication. The first two new DAAs were protease inhibitors, telaprevir and boceprevir, and they were approved in combination with Peg-INF/RBV for genotype 1 patients. Recently, two new DAA agents have been approved by Health Canada (simeprevir and sofosbuvir). Simeprevir is a protease inhibitor, while sofosbuvir employs a novel mechanism of action, targeting an HCV polymerase. Sofosbuvir is the only DAA to be approved for genotypes 2, 3, and 4, in addition to genotype 1.

1.3 Drug

Indication under review
SOVALDI (sofosbuvir) is indicated for the treatment of chronic hepatitis C (CHC) virus infection in adult patients with compensated liver disease, including cirrhosis, as follows: • For the treatment of genotype 1 and genotype 4 CHC infection in combination with pegylated interferon plus ribavirin (Peg-INF/RBV); • For the treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin.
Listing criteria requested by sponsor
Gilead is requesting that sofosbuvir receive a positive listing recommendation for the treatment of patients with CHC based on the following criteria: • Treatment-naive patients with chronic hepatitis C virus (HCV) genotype 1 infection; • Peg-INF/RBV-experienced patients with chronic HCV genotype 2 infection; • Peg-INF/RBV-experienced patients with chronic HCV genotype 3 infection; and • Genotype 2 and 3 CHC patients for whom interferon is medically contraindicated.

TABLE 3: KEY CHARACTERISTICS OF SIMEPREVIR, BOCEPREVIR, TELAPREVIR, AND SOFOSBUVIR

	Simeprevir	Boceprevir	Telaprevir	Sofosbuvir
Mechanism of Action	DAA against the HCV that is a specific inhibitor of the HCV NS3·4A protease through a non-covalent, induced-fit binding into the active site of the NS3 protease	DAA against the HCV that is a specific inhibitor of the HCV NS3/4A protease, covalently, yet reversibly binds to the NS3/4A protease active site serine (Ser139) through a (alpha)-ketoamide functional group to inhibit viral replication in HCV-infected host cells	DAA against the HCV that is a specific inhibitor of the HCV NS3·4A protease, which is essential for viral replication	DAA against the HCV that is mediated by a membrane-associated multi-protein replication complex. The HCV polymerase (NS5B protein) is an RNA-dependent RNA polymerase and is the essential initiating and catalytic subunit of this replication complex and is critical for the viral replication cycle
Indication[a]	Treatment of CHC genotype 1 infection, in combination with Peg-INF/RBV in adults with compensated liver disease, including cirrhosis, who are treatment-naive or who have failed previous interferon therapy (pegylated or non-pegylated) with ribavirin	Treatment of CHC genotype 1 infection, in combination with Peg-INF/RBV, in adult patients (18 years or older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous therapy	Treatment of CHC genotype 1 infection, in combination with Peg-INF/RBV, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers	Treatment of genotype 1 and genotype 4 CHC infection in combination with Peg-INF/RBV and treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin

	Simeprevir	Boceprevir	Telaprevir	Sofosbuvir
Route of Administration	Oral			
Recommended Dose	150 mg capsule once daily with Peg-INF/RBV **Treatment-naive:** triple therapy for 12 weeks, followed by Peg-INF/RBV for additional 12 or 36 weeks based on RGT **Treatment-experienced:** triple therapy for 12 weeks, plus Peg-INF/RBV for additional 12 or 36 weeks based on RGT (prior-relapsers), or for an additional 36 weeks (prior partial and null responders) **Cirrhotic patients**: As per above; no special dosing.	800 mg (four 200 mg capsules) three times daily with Peg-INF/RBV **Treatment-naive:** Peg-INF/RBV therapy for 4 weeks, triple therapy for 24 weeks, Peg-INF/RBV therapy for a possible additional 20 weeks based on RGT **Treatment-experienced:** Peg-INF/RBV therapy for 4 weeks, and either triple therapy for 32 weeks or triple therapy for 32 weeks plus Peg-INF/RBV for an additional 12 weeks, based on RGT (Prior relapse and prior partial responders) or triple therapy for 44 weeks (prior null responders). **Cirrhotic patients:** Peg-INF/RBV therapy for 4 weeks and triple therapy for 44 weeks.	1,125 mg (three 375 mg tablets) twice daily in combination with Peg-INF/RBV **Treatment-naive:** triple therapy for 12 weeks, Peg-INF/RBV therapy for additional 12 or 36 weeks based on RGT **Treatment-experienced:** triple therapy for 12 weeks, Peg-INF/RBV for additional 12 or 36 weeks based on RGT (prior-relapsers) or triple therapy for 12 weeks, Peg-INF/RBV for additional 36 weeks (prior partial and null responders). **Cirrhotic patients:** triple therapy for 12 weeks, Peg-INF/RBV for additional 36 weeks.	**Genotypes 1 and 4:** 400 mg tablet, once daily with Peg-INF/RBV for 12 weeks **Genotype 2:** 400 mg tablet once daily in combination with RBV for 12 weeks **Genotype 3:** 400 mg tablet once daily in combination with RBV for 16 weeks. Consideration should be given to extending the duration of therapy beyond 16 weeks and up to 24 weeks, guided by an assessment of the potential benefits and risks for the individual patient (these factors may include cirrhosis status and treatment history).
Serious Side Effects/Safety Issues	Photosensitivity, sunburn, blistering, redness of the skin, swelling of the skin	Anemia, neutropenia, skin reactions	Anemia, skin reactions	Anemia, neutropenia, thrombocytopenia

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; Peg-INF = pegylated interferon; Peg-INF/RBV = pegylated interferon plus ribavirin; RBV = ribavirin; RGT = response-guided therapy.
[a]Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of sofosbuvir in combination with other agents for the treatment of adults with CHC infection (genotypes 1, 2, 3, or 4).

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to the Common Drug Review (CDR), as well as those meeting the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with CHC infection (genotypes 1, 2, 3, or 4) with compensated liver disease including cirrhosis **Subpopulation:** • Treatment history based on prior Peg-INF/RBV (treatment naive, prior relapse, prior partial response, null response) • Fibrosis level • HIV coinfection • Genotype subtype • Interferon-intolerant, interferon ineligible, or unwilling to take interferon • Liver transplant recipients
Intervention[a]	**Genotypes 1 or 4**: Sofosbuvir 400 mg once daily in combination with Peg-INF/RBV[b] **Genotypes 2 or 3**: Sofosbuvir 400 mg once daily in combination with ribavirin
Comparators[a]	**Genotype 1** • Placebo in combination with Peg-INF/RBV[b] • Boceprevir in combination with Peg-INF/RBV[b] • Telaprevir in combination with Peg-INF/RBV[b] • Simeprevir in combination with Peg-INF/RBV[b] • Placebo or no treatment **Genotypes 2, 3, or 4** • Placebo in combination with Peg-INF/RBV[b] • Placebo or no treatment
Outcomes	**Key efficacy outcomes:** • Sustained virologic response • Relapse • HRQoL measured with a validated scale • Mortality (all-cause and liver-related) **Other efficacy outcomes:** • Hepatic-related morbidity outcomes (e.g., histological changes, hepatocellular carcinoma, liver failure, liver transplant) **Harms outcomes:** • SAE, WDAE, AE • Harms of special interest (rash, fatigue, anemia, neutropenia, pruritus, depression, sleep loss, nausea, photosensitivity)
Study Design	Published and unpublished RCTs

AE = adverse event; CHC = chronic hepatitis C; HRQoL = health-related quality of life; Peg-INF/RBV = pegylated interferon plus ribavirin; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a]At Health Canada–recommended dosing regimens.
[b]Either pegylated interferon alpha-2a or pegylated interferon alpha-2b.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–)through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were sofosbuvir and Sovaldi.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on March 10, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on July 16, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials, and databases (free). Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

3. RESULTS

3.1 Findings from the Literature

A total of five studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 and Table 6 and described in section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

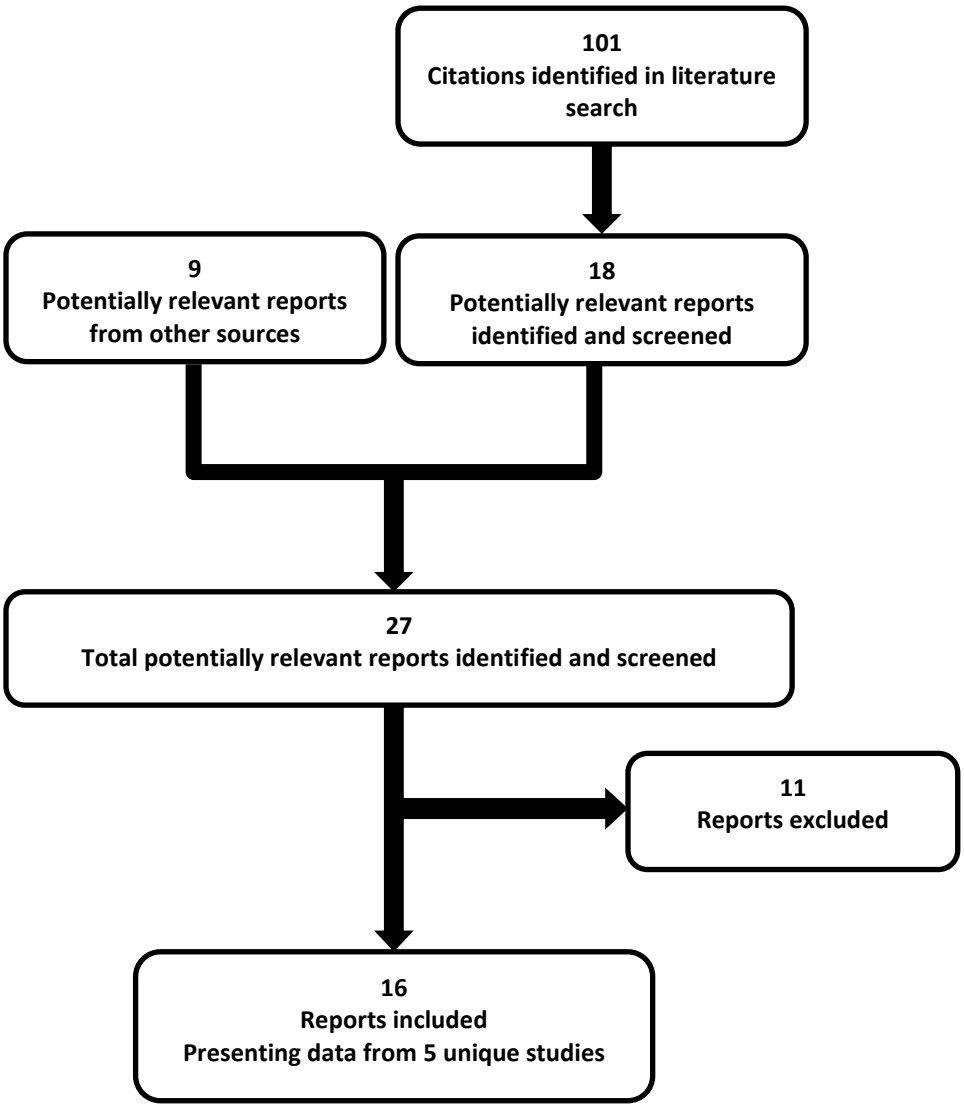


TABLE 5: DETAILS OF INCLUDED STUDIES OF GENOTYPES 1 AND 4

		NEUTRINO
DESIGNS & POPULATIONS	**Study Design**	Single group
	Locations	56 centres: USA
	Study Period	June 2012 to January 2013
	Enrolled	N = 327
	Inclusion Criteria	Genotype 1, 4, 5, or 6 HCV treatment-naive Serum HCV RNA ≥ 10^4 IU/mL 20% of patients could have evidence of cirrhosis
	Exclusion Criteria	HIV or HBV
DRUGS	**Intervention**	Sofosbuvir 400 mg PO daily, ribavirin[a] + pegylated interferon alpha-2a 180 mcg SC once weekly for 12 weeks
	Comparator(s)	None
DURATION	Screening	4 weeks
	Treatment	12 weeks
	Follow-up	Up to 24 weeks (shorter with relapse)
OUTCOMES	**Primary End Point**	SVR12
	Other End Points	Proportion of patients with HCV RNA < LLOQ by study visit HCV RNA absolute values and change from baseline in HCV RNA through week 8 ALT normalization HRQoL (SF-36, CLDQ-HCV, FACIT-F, and WPAI-Hep C)
NOTES	**Publications**	Lawitz 2013,[28] Younossi 2013,[29] Younossi 2014[30,31]

ALT = alanine aminotransferase; BMI = body mass index; CLDQ-HCV = Chronic Liver Disease Questionnaire — Hepatitis C Virus; FACIT-F = Functional Assessment of Chronic Illness Therapy—Fatigue; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV=human immunodeficiency virus; HRQoL = health-related quality of life; LLOQ = lower limit of quantification; Peg-INF = pegylated interferon; PO = orally; RNA = ribonucleic acid; SC = subcutaneous; SF-36 = Short-Form 36; SVR = sustained virologic response; ULN = upper limit normal; WPAI-HepC = Work Productivity and Activity Impairment — Hepatitis C.
[a]Ribavirin was dosed by weight: patients < 75kg received 1,000 mg; ≥ 75kg, 1,200 mg.
Source: Clinical Study Report for NEUTRINO.[15]

TABLE 6: DETAILS OF INCLUDED STUDIES FOR GENOTYPES 2 AND 3

		FISSION	VALENCE	FUSION	POSITRON
DESIGNS & POPULATIONS	**Study Design**	OL RCT	DB RCT initially, then OL	DB RCT	DB RCT
	Locations	90 centres: USA, Australia, New Zealand, Canada, Europe	Europe	57 centres: USA, Canada, New Zealand	56 centres: USA
	Study Period	December 2011 to January 2013	Sep 19, 2013 to Oct 2, 2013 (interim)	June 2012 to February 2013	March 2012 to November 2012
	Randomized (N)	N = 527	N = 419	N = 201	N = 280
	Inclusion Criteria	Genotype 2 or 3 HCV treatment-naive Serum HCV RNA ≥ 10^4 IU/mL Up to 20% of patients could have cirrhosis	Genotype 2 or 3 HCV treatment-naive (no prior INF) or experienced (INF-intolerant[a] or failed) Serum HCV RNA ≥ 10^4 IU/mL	Genotype 2 and 3 Prior treatment failure with ≥ 12 weeks Peg-INF with or without ribavirin Serum HCV RNA ≥ 10^4 IU/mL	Genotype 2 and 3 Peg-INF–ineligible, –intolerant, or –unwilling Serum HCV RNA ≥ 10^4 IU/mL 20% of patients could have evidence of cirrhosis
	Exclusion Criteria	HIV or HBV coinfection	Nothing of note	HIV or HBV coinfection	HIV or HBV coinfection
DRUGS	**Intervention**	Sofosbuvir 400 mg PO daily + ribavirin[b] for 12 weeks	Genotype 2: Sofosbuvir 400 mg PO daily + ribavirin[b] for 12 weeks Genotype 3: Sofosbuvir 400 mg PO daily + ribavirin[b] for 24 weeks	Sofosbuvir 400 mg PO once daily + ribavirin[a] for 12 weeks, followed by Sofosbuvir placebo administered once daily + ribavirin placebo for 4 weeks	Sofosbuvir 400 mg PO once daily + ribavirin[a] for 12 weeks
	Comparator(s)	Peg-INF 180 mcg SC weekly + ribavirin 800 mg daily for 24 weeks	Placebo for 12 weeks	Sofosbuvir 400 mg PO once daily +ribavirin[a] for 16 weeks	Placebo for 12 weeks
DURATION	**Phase**				
	Screening	Up to 6 weeks		4 weeks	6 weeks
	Treatment period	12 or 24 weeks	12 or 24 weeks	16 weeks	12 weeks
	Follow-up	Up to 24 weeks	12 weeks	Up to 24 weeks (shorter with relapse)	Up to 24 weeks (shorter with relapse)
OUTCOMES	**Primary End Point**	SVR12	SVR12	SVR12	SVR12
	Other End Points	Patients with HCV RNA < LLOQ by study visit Absolute values and change from baseline, HCV RNA through week 12	Virologic failure, relapse	SVR4 and SVR24 Proportion of patients with HCV RNA < LLOQ by study visit HCV RNA absolute values and	Patients with HCV RNA < LLOQ by study visit Absolute values and change from baseline in HCV RNA through

		FISSION	VALENCE	FUSION	POSITRON
		Virologic failure (including relapse) ALT normalization Time to first HCV RNA < LLOQ and time to first HCV RNA < LLOQ HRQoL (SF-36)		change from baseline in HCV RNA through week 8 Virologic failure (including relapse) Resistance analysis; ALT normalization HRQoL (SF-36, CLDQ-HCV, FACIT-F, and WPAI-HepC)	week 8 Virologic failure (including relapse) ALT normalization HRQoL (SF-36)
NOTES	**Publications**[c]	Lawitz 2013,[28] Younossi 2013,[29] Younossi 2014[30]	Younossi 2014,[32] Zeuzem 2014[20]	Jacobson 2013,[33] Younossi 2014[30,31]	Jacobson 2013,[33] Younossi 2014[30]

ALT = alanine aminotransferase; BMI = body mass index; CLDQ-HCV = Chronic Liver Disease Questionnaire — Hepatitis C Virus; DB = double-blind; FACIT-F = Functional Assessment of Chronic Illness Therapy — Fatigue; HBV = hepatitis B virus; HCV = hepatitis C virus; HRQoL = health-related quality of life; INF = interferon; Peg-INF = pegylated interferon; LLOQ = lower limit of quantification; OL = open-label; PO = orally; RNA = ribonucleic acid; SC = subcutaneous; SVR = sustained virologic response; SVR12 = sustained virologic response, 12 weeks; ULN = Upper Limit Normal; WPAI-Hep C = Work Productivity and Activity Impairment — Hepatitis C.

[a]Interferon intolerance was defined as a patient having discontinued ≤ 12 weeks of INF-containing HCV treatment (≥ 3 months prior to screening) due to the development or significant worsening of at least 1 of a number of protocol-specified conditions associated with INF toxicity.

[b]Ribavirin was dosed by weight: patients < 75kg received 1,000 mg; ≥ 75kg received 1,200 mg.

[c]Nine additional reports were included: Health Canada Reviewers Report,[34] FDA Clinical and Statistical Review,[35,36] manufacturer's submission,[37] and clinical study reports for the included studies.[15-19]

Source: Clinical Study Reports for FISSION,[16] VALENCE,[17] FUSION,[18] and POSITRON.[19]

3.2 Included Studies

3.2.1 Description of Studies

Five studies met the inclusion criteria for this systematic review, four of which (NEUTRINO, FISSION, FUSION, and POSITRON) were considered pivotal. All studies were multi-centre. FUSION and FISSION had sites across multiple countries, while the others were based in the USA.

One study (NEUTRINO) was a single-arm study that enrolled patients with genotypes 1, 4, 5, and 6. The other four studies were RCTs that enrolled patients with genotypes 2 and 3 (FUSION, POSITRON, FISSION, and VALENCE).

Of the four RCTs enrolling patients with genotypes 2 and 3, one was an open-label non-inferiority study (FISSION) that compared sofosbuvir+ribavirin to Peg-INF/RBV. The remaining three studies were double-blinded, with one comparing sofosbuvir+ribavirin with placebo (POSITRON), one comparing two different durations of sofosbuvir+ribavirin (FUSION), and one study that included two different durations of sofosbuvir+ribavirin (a 12-week regimen for genotype 2 and a 24-week regimen for genotype 3 patients), and also had a placebo group (VALENCE).

VALENCE was initially designed as a DB RCT to compare 12 weeks of sofosbuvir+ribavirin with placebo. However, as data from FUSION suggested that genotype 3 patients may benefit from a longer regimen, the protocol for VALENCE was changed during the study to extend the treatment duration of sofosbuvir+ribavirin from 12 to 24 weeks in genotype 3 patients, provided they had not already completed the 12-week course. The placebo group was halted, and the remaining groups were unblinded and the study became a descriptive study, with two remaining groups, both treated with sofosbuvir+ribavirin (genotype 2 had a 12-week regimen; genotype 3 had a 24-week regimen).

FISSION tested the non-inferiority of sofosbuvir+ribavirin versus Peg-INF/RBV, while POSITRON tested the superiority of sofosbuvir+ribavirin to placebo. After confirming that the proportion of patients achieving SVR12 had exceeded a minimal threshold (25%), FUSION tested the superiority of a 16-week sofosbuvir+ribavirin regimen versus a 12-week sofosbuvir+ribavirin regimen.

Patients in all the RCTs were randomized by use of an interactive voice response system. In FISSION, the randomization scheme was stratified by genotype (2 or 3), screening HCV RNA level (< 6 log10 IU/mL or ≥ 6 log10 IU/mL), and cirrhosis (presence or absence). Patients with genotype 2 or 3 HCV infection were enrolled in an approximately 1:3 ratio. In FUSION, randomization was stratified by the presence or absence of cirrhosis and HCV genotype (2 or 3) at screening. In POSITRON, the randomization scheme was stratified by the presence or absence of cirrhosis at screening. The VALENCE study was originally stratified for previous therapy (no prior therapy or prior therapy), and cirrhosis (presence or absence). However, after the protocol amendment described above, VALENCE became a descriptive study that was not designed to test hypotheses.[20]

Blood samples were collected to determine serum levels of HCV RNA at screening and at each study visit during the treatment and post-treatment periods. The COBAS TaqMan HCV Test v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study. The lower limit of quantification (LLOQ) of the assay was 25 IU/mL. Health-related quality of life (HRQoL) assessments were performed at baseline; weeks 12, 16, and 24 (where applicable); end of therapy; and 12 and 24 weeks after the end of therapy. FUSION also assessed HRQoL at week four, and post-treatment at weeks four and eight. NEUTRINO also assessed at post-treatment week four. Because in these short-term studies, quality of life is most affected during treatment, the end-of-therapy findings are reported in this review.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Two of the included studies enrolled only treatment-naive patients (NEUTRINO, FISSION), while FUSION enrolled patients who were prior treatment failures (either prior treatment with pegylated interferon or pegylated interferon+ribavirin) and POSITRON enrolled patients who were either pegylated interferon-intolerant, ineligible, or unwilling to take pegylated interferon. Patients in VALENCE could be either treatment naive or experienced.

All studies included patients with cirrhosis, although all of those but FUSION and VALENCE restricted cirrhotic patients to 20% of the population. FUSION and VALENCE did not have any restrictions on cirrhosis at baseline.

All studies except VALENCE specifically excluded patients coinfected with either HBV or HIV. VALENCE did not specify HBV or HIV as an exclusion criterion.

b) Baseline Characteristics

In NEUTRINO, the majority of patients (89%) were genotype 1, and 9% were genotype 4. The mean age was 52 years, 64% were male, and approximately 17% of patients had cirrhosis (Table 7).

Among studies conducted in patients with genotypes 2 or 3 (Table 8), the mean age of patients ranged from late 40s to early 50s (48 to 54 years of age). The oldest patient population was in FUSION, which was also the only study to feature patients who had all failed previous treatment with either pegylated interferon or Peg-INF/RBV. The majority of patients were male, in most groups in most studies. In POSITRON, there were approximately equal proportions of genotypes 2 and 3, while in FUSION and FISSION, genotype 3 made up approximately two-thirds of the population. VALENCE was the only study to randomize genotype 2 and 3 patients into separate groups, and there were 261 genotype 3 patients and 73 genotype 2 patients. The study with the highest proportion of cirrhotic patients at baseline was FUSION (34%), with no restrictions on the number of patients with cirrhosis. In the other pivotal studies, the prevalence of cirrhosis was around 20%, consistent with the protocol restriction.

Baseline characteristics such as HCV RNA were generally similar between groups. There were some differences with respect to gender, with a higher proportion of males in the sofosbuvir+ribavirin group versus placebo in POSITRON (57% versus 48%). In VALENCE, there were differences with respect to age, largely driven by the fact that genotype 2 patients were older than genotype 3 patients (58 versus 48 years old).

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS IN STUDIES OF GENOTYPES 1 AND 4

	NEUTRINO Naive G1, G4, G5, G6
	SOF12+Peg-INF/RBV12 N = 327
Mean age, years (SD)	52 (10)
Male, n (%)	209 (64)
HCV subtype, n (%):	
1a	225 (69)[a]
1b	66 (20)
2	0
3	0
4	28 (9)
5	1 (< 1)
6	6 (2)
Mean (SD) HCV RNA, $\log_{10}$ IU/mL	6.4 (0.7)
IL28B genotype, n (%)	
CC allele	95 (29)
CT allele	181 (55)
TT allele	51 (16)
Cirrhosis, n (%)	54/324[b] (17)

G = genotype; HCV = hepatitis C virus; RNA = ribonucleic acid; SD = standard deviation; SOF12+Peg-INF/RBV12 = 12 weeks sofosbuvir + 12 weeks pegylated interferon plus ribavirin.
[a]One patient had mixed subtype 1a/1b infection.
[b]Data missing on 3 patients.
Source: Clinical Study Report for NEUTRINO.[15]

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS FOR GENOTYPES 2 AND 3

	FISSION Naive G2, G3		POSITRON INF-Intolerant, -Unwilling, -Ineligible G2, G3		FUSION Failure G2, G3		VALENCE Naive or Experienced G2, G3			
	SOF12RBV12 N = 256	Peg-INF/ RBV24 N = 243	SOF12RBV12 N = 207	PLAC12 N = 71	SOF12RBV12 N = 103	SOF16RBV16 N = 98	SOF12RBV12 G2 N = 73	SOF12RBV12 G3 N = 11	SOF24RBV24 G3 N = 250	PLAC12 N = 85
Mean age, years (SD)	48 (10.8)	48 (11.4)	52 (9.9)	52 (8.2)	54 (7.7)	54 (7.8)	58 (10.1)	46 (8.8)	48 (10.1)	49 (10.5)
Male, n (%)	171 (67)	156 (64)	117 (57)	34 (48)	73 (71)	67 (68)	40 (55)	6 (55)	155 (62)	49 (58)
HCV subtype, n (%):										
1	3 (1)	0			3 (3)	3 (3)				
2	70 (27)	67 (28)	109 (53)	34 (48)	36 (35)	32 (33)	73 (100)	0	0	18 (21)
3	183 (72)	176 (72)	98 (47)	37 (52)	64 (62)	63 (64)	0	11 (100)	250 (100)	67 (79)
4										
5										
6										
Mean (SD) HCV RNA, $\log_{10}$ IU/mL	6.0 (0.8)	6.0 (0.8)	6.3 (0.8)	6.3 (0.8)	6.5 (0.7)	6.5 (0.6)	6.5 (0.7)	6.2 (0.8)	6.3 (0.7)	6.5 (0.7)
IL28B genotype, n (%)										
CC allele					31 (30)	30 (31)	24 (33)	4 (36)	86 (34)	22 (26)
CT allele					53 (52)	56 (57)	41 (56)	4 (36)	131 (52)	49 (58)
TT allele					19 (18)	12 (12)	8 (11)	3 (27)	33 (13)	14 (17)
Cirrhosis, n (%)	50 (20)	50 (21)	31 (15)	13 (18)	36 (35)	32 (33)	10 (14)	2 (18)	58 (23)	18 (21)
INF-ineligible			88 (43)	33 (47)						
INF-intolerant			17 (8)	8 (11)						
INF-unwilling			102 (49)	30 (42)						
INF-experienced							41 (56)	9 (82)	145 (58)	50 (59)

G = genotype; HCV = hepatitis C virus; INF = interferon; IU = International units; PLAC12 = 12 weeks placebo; Peg-INF/RBV24 = 24 weeks pegylated interferon + ribavirin; RNA = ribonucleic acid; SD = standard deviation; SOF12RBV12 = 12 weeks sofosbuvir + 12 weeks ribavirin; SOF16RBV16 = 16 weeks sofosbuvir + 16 weeks ribavirin; SOF24RBV24 = 24 weeks sofosbuvir + 24 weeks ribavirin.
Source: Clinical Study Reports for FISSION,[16] VALENCE,[17] FUSION,[18] POSITRON.[19]

3.2.3 Interventions

In all studies, sofosbuvir was administered for 12 weeks in at least one of the groups. In the NEUTRINO study (genotypes 1, 4, 5, and 6), all patients received sofosbuvir+Peg-INF/RBV for 12 weeks. In studies enrolling patients with genotype 2 and 3, sofosbuvir was combined with ribavirin, with some slight variations between studies, as described below:

a) Treatment-Naive

- FISSION: sofosbuvir+ribavirin for 12 weeks (comparator: Peg-INF/RBV for 24 weeks)

b) Treatment-Experienced

- FUSION: sofosbuvir+ribavirin for 12 weeks, then placebo for 4 weeks (comparator: sofosbuvir+ribavirin for 16 weeks)

c) Intolerant of or Ineligible or Unwilling to Take Peginterferon

- POSITRON: sofosbuvir+ribavirin for 12 weeks (comparator: placebo for 12 weeks)

d) Mixed (Naive and Experienced)

- VALENCE: based on genotype:
  - genotype 2: sofosbuvir+ribavirin for 12 weeks
  - genotype 3: sofosbuvir+ribavirin for 24 weeks
  - the comparator for both genotypes was originally placebo

In VALENCE, the 24-week regimen was added as a protocol amendment while the study was ongoing. Initially, both genotype 2 and 3 patients were to receive 12 weeks of sofosbuvir+ribavirin, but after observing results from the FUSION study, the manufacturer hypothesized that genotype 3 patients might benefit from a longer, 24-week regimen of sofosbuvir+ribavirin. Because the amendment was made while the study was ongoing, genotype 3 patients who had completed 12 weeks of sofosbuvir+ribavirin were considered to have completed their regimen, and were considered a separate group, while patients who had not yet reached 12 weeks of treatment continued taking their regimen until they reached 24 weeks of therapy. The placebo group was halted and were not part of the efficacy analysis.

3.2.4 Outcomes

The primary efficacy end point for all studies was the proportion of patients with SVR 12, defined as HCV RNA < LLOQ 12 weeks after stopping all study drugs.

Relapse was defined as having HCV RNA ≥ LLOQ during the post-treatment period, having achieved HCV RNA < LLOQ at end of treatment, confirmed with two consecutive values or last available post-treatment measurement.

Resistance testing: population sequencing of the nucleotide HCV non-structural 5B (NS5B) was performed using standard sequencing technology on all baseline viral samples. Deep sequencing of HCV NS5B was performed for patients who did not achieve SVR (virologic failures) and had HCV RNA > 1,000 IU/mL at virologic failure with plasma sample available for analysis. Amino acid substitutions in NS5B in the samples collected at virologic failure were compared with the respective baseline sequence for each patient. HCV phenotypic assays were performed for observed NS5B substitutions in representative samples.

The Chronic Liver Disease Questionnaire (CLDQ) is an HRQoL instrument for patients with chronic liver disease. CLDQ measures Activity/Energy, Emotion, Worry, Systemic, and CLDQ total score. All domains and total score are based on a Likert scale of 0 (worse) to 7 (best).[38] The Functional Assessment of Chronic Illness Therapy — Fatigue scale (FACIT-F) is a 40-item scale assessing fatigue and its impact on daily activities. Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale, make up the total score, ranging from 0 (worst) to 160 (best). The Work Productivity and Activity Impairment (WPAI) questionnaire is an instrument used to measure the impact of a disease on work and on daily activities. Work impairment domain is the sum of impairment in work productivity due to absenteeism (productivity loss due to a health-related absence from work, including personal time off, sick days off work, duration of short- or long-term disability, or worker's compensation days) and impairment due to decreased productivity while at work (reduced performance of productivity while at work due to health reasons, including time not being on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work.[39]

The period of observation for collection of AEs extended from the first dose of study drug until the visit 28 weeks after the baseline visit or four weeks after an early termination visit.

All SAEs were collected from the time of informed consent until the visit 28 weeks after the baseline visit or four weeks after an early termination visit. They were followed until resolution.

3.2.5 Statistical Analysis

Although NEUTRINO was a single-arm trial, the statistical analysis included a comparison to an external control, as described below. The primary efficacy analysis assessed whether patients who were administered sofosbuvir+ Peg-INF/RBV for 12 weeks achieved an SVR12 greater than 60%. The basis for the 60% SVR null proportion was derived from:

- an historical SVR proportion of approximately 65% calculated from the telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data after adjusting for the targeted proportion of patients with cirrhosis (approximately 20%) in NEUTRINO; and
- a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment.

The weighted average of the telaprevir and boceprevir data was estimated to be approximately 70% in non-cirrhotic patients, and 44% in cirrhotic patients. The SVR proportion for the control in this study (i.e., a patient population of 80% non-cirrhotic and 20% cirrhotic) was then calculated to be approximately 65% (i.e., 0.8 × 70% + 0.2 × 44%). As noted above, the 60% null SVR proportion was obtained after allowing for a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter treatment duration. In NEUTRINO, the planned sample size was 300 patients. A sample size of 300 patients provided 90% power to detect a 9% improvement in SVR12 from 60% to 69% using a two-sided one-sample binomial test at a significance level of 0.05.

In FISSION, a closed testing procedure was utilized whereby the non-inferiority of sofosbuvir+ribavirin to Peg-INF/RBV was tested first. Non-inferiority was assessed using a conventional 95% confidence interval (CI) approach, with a delta of 0.15. According to the manufacturer, the margin was based on the smallest treatment difference between ribavirin alone and Peg-INF/RBV. It also allowed that at least part of the treatment effect of Peg-INF/RBV (standard therapy) was preserved for sofosbuvir+ribavirin. If the lower bound of the two-sided 95% CI on the difference (sofosbuvir+ribavirin treatment group minus Peg-INF/RBV treatment group) in the response was ≥ 15%, then it was to be concluded that sofosbuvir+ribavirin was non-inferior to Peg-INF/RBV. If the non-inferiority null hypothesis was rejected,

then the *P* value associated with the test of superiority was calculated. Superiority would have been demonstrated if the two-sided *P* value was < 0.05. In FISSION, the planned sample size of 500 patients (250 in each treatment group) was estimated to provide > 95% power to establish non-inferiority of sofosbuvir+ribavirin treatment relative to Peg-INF/RBV in the proportion of patients with SVR12. For the sample size calculation, it was assumed that both the sofosbuvir+ribavirin and Peg-INF/RBV groups had a response of 75% and that the non-inferiority margin was 15%. A sample size of 250 per group would provide 93% power to detect a 12% difference in SVR12 between the treatment groups (sofosbuvir+ribavirin and Peg-INF/RBV group) using a two-sided chi-squared test and a significance level of 0.05 (assuming an SVR12 of 75% in the Peg-INF/RBV group).

In FUSION, the two primary statistical hypotheses of the study were that the proportion of patients with an SVR12 in both treatment groups (sofosbuvir+ribavirin for 12 weeks and sofosbuvir+ribavirin for 16 weeks) was higher than 25%. The 95% exact CI based on a Clopper-Pearson method was provided for the SVR12 proportion in each of the two treatment groups. Both hypotheses were tested at a significance level of 0.025 using a Bonferroni correction to adjust for multiple testing. If the tests in the primary analysis were statistically significant at the 0.025 significance level, the secondary analysis of comparing the SVR12 proportions between the two treatment groups was performed using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factors (i.e., presence or absence of cirrhosis; genotype 2 or 3). In FUSION, a sample size of 100 patients in each group provided more than 97% power to detect at least a 20% improvement in the SVR12 from the assumed null of 25% using a two-sided, exact, one-sample, binomial test at a significance level of 0.025. In addition, this sample size also provided 82% power to detect a difference of 20% in SVR12 (50% versus 70%) between the 12- and 16-week treatment groups.

In POSITRON, the primary efficacy analyses assessed whether sofosbuvir+ribavirin achieved superiority over placebo with respect to the proportion of patients achieving SVR12. The proportions of patients achieving SVR12 between the two groups (versus placebo) were compared using a Cochran–Mantel–Haenszel (CMH) test stratified by the absence or presence of cirrhosis. Superiority was demonstrated if the two-sided CMH test result with *P* value was < 0.05. The difference in SVR12 between groups and associated 95% CI were calculated based on stratum-adjusted Mantel–Haenszel proportions. In POSITRON, a sample size of 180 patients in the active group and 60 patients in the placebo group provided 99% power to detect a 40% difference between-group SVR12 using a two-sided continuity-corrected chi-square test at a significance level of 0.05.

In VALENCE, there was a fundamental change in the protocol as previously described. The efficacy analysis was adjusted to now reflect the new design, with 12- and 24-week sofosbuvir+ribavirin genotype 3 groups and a 12-week genotype 2 group. The manufacturer noted that there were no SVR12 responses in placebo; thus, this group was not reported in data summary tables. The composition of the groups differed for the safety analysis, as the placebo group was included in this analysis, and the sofosbuvir+ribavirin patients were grouped based on treatment duration (i.e., genotypes were not analyzed separately).

In all studies, a missing SVR value was imputed as a success if it was bracketed by values that were termed successes (i.e., "< LLOQ target not detected" or "< LLOQ detected"); otherwise, the missing SVR value was imputed as a failure.

a) Analysis Populations

In all trials, the full analysis set was defined as HCV infection patients who were randomized into the study and received at least one dose of study medication. If baseline sequencing determined that a patient was not actually the correct genotype, they were excluded from the full analysis set. The safety population was defined as any patient who received at least one dose of study drug. The per-protocol analysis set included patients in the full analysis set who met all eligibility criteria and who had no major protocol deviations during the study.

3.3 Patient Disposition

In NEUTRINO, 11% of patients discontinued the study, the most common reason being efficacy failure (Table 9).

The rate of study withdrawals differed between groups in all studies reporting (Table 10). In FISSION, 28% of Peg-INF/RBV patients withdrew, compared with 13% of sofosbuvir+ribavirin patients. This difference was accounted for by a large difference in efficacy failures (21% versus 1%, respectively). In FUSION, the study withdrawal rate was high in both groups, but higher with the 12-week than the 16-week regimen (51% versus 30%). FUSION was the study that enrolled previous treatment failures, and efficacy failure again accounted for almost all of the withdrawals. In POSITRON, all patients in the placebo group discontinued from the study, and all of these withdrawals were due to efficacy failure.

TABLE 9: PATIENT DISPOSITION IN STUDIES OF GENOTYPES 1 AND 4

	NEUTRINO
	SOF12+Peg-INF/RBV12 (N = 327)
Screened	456
Enrolled	328
Enrolled and treated	327
Safety set	327
Full analysis set	327
Per-protocol	NR
Completed treatment	320 (98)
Discontinued tx, n (%)	7 (2)
Adverse event	5 (2)
Protocol violation	1 (< 1)
Withdrew consent	1 (< 1)
Lost to follow-up	0
Death	0
Viral failure	0
Other	0
Discontinued study, n (%)	35 (11)
Efficacy failure	29 (9)
Lost to follow-up	3 (1)
Withdrew consent	2 (1)
Other	0
Non-protocol HCV Tx	0
Death	0
Completed study	292 (89)

HCV = hepatitis C virus; SOF12+Peg-INF/RBV12 = 12 weeks sofosbuvir + 12 weeks pegylated interferon plus ribavirin; Tx = treatment.
Source: Clinical Study Report for NEUTRINO.[15]

TABLE 10: PATIENT DISPOSITION FOR GENOTYPES 2 AND 3

	FISSION		POSITRON INF-intolerant, unwilling, ineligible G2, G3		FUSION Failure G2, G3		VALENCE Naive or experienced G2, G3			
	SOF12RBV12 N = 256	Peg-INF/RBV24 N = 243	SOF12RBV12 N = 207	PLAC12 N = 71	SOF12RBV12 N = 103	SOF16RBV16 N = 98	SOF12RBV12 G2 N = 73	SOF12RBV12 G3 N = 11	SOF24RBV24 G3 N = 250	PLAC12 N = 85
Screened	666		410		277		475			
Enrolled	263	264	209	71	103	99	NR	NR	NR	NR
Enrolled and treated	256	243	207	71	103	98	NR	NR	NR	NR
Safety set	256	243	207	71	103	98	73	11	250	85
Full analysis set	253	243	207	71	100	95	73	11	250	0
Per-protocol	246	231								
Completed treatment	245 (96)	189 (78)	201 (97)	68 (96)	102 (99)	98 (100)	73 (100)	8 (73)	246 (98)	4 (5)
Discontinued tx, n (%)	11 (4)	54 (22)	6 (3)	3 (4)	1 (1)	0	0	3 (27)	4 (2)	81 (95)
Adverse event	3 (1)	26 (11)	4 (2)	3 (4)	1 (1)	0	0	1 (9)	1 (< 1)	1 (1)
Protocol violation	0	0	0	0	0	0	0	0	0	0
Withdrew consent	1 (< 1)	2 (< 1)	0	0	0	0	0	2 (18)	2 (1)	0
Lost to follow-up	2 (< 1)	5 (2)	2 (1)	0	0	0	0	0	1 (< 1)	1 (1)
Death	1 (< 1)	0	0	0	0	0	0	0	0	0
Viral failure	1 (< 1)	17 (7)	0	0	0	0	0	0	0	0
Other	3 (1)	4 (2)	0	0	0	0	0	0	0	0
Terminated by sponsor	0	0	0	0	0	0	0	0	0	79 (93)
Discontinued study, n (%)	32 (13)	67 (28)	53 (26)	71 (100)	52 (51)	29 (30)	NR	NR	NR	NR
Efficacy failure	2 (1)	50 (21)	41 (20)	71 (100)	50 (49)	29 (30)	NR	NR	NR	NR
Lost to follow-up	11 (4)	10 (4)	5 (2)	0	1 (1)	0	NR	NR	NR	NR
Withdrew consent	6 (2)	6 (3)	1 (< 1)	0	1 (1)	0	NR	NR	NR	NR
Other	5 (2)	0	0	0	0	0	NR	NR	NR	NR
Non-protocol HCV Tx	7 (3)	0	2 (1)	0	0	0	NR	NR	NR	NR
Death	1 (< 1)	1 (< 1)	3 (1)	0	0	0	NR	NR	NR	NR
On study	0	0	0	0	0	0	NR	NR	NR	NR
Completed study	224 (88)	176 (72)	154 (74)	0	51 (49)	69 (70)	NR	NR	NR	NR

HCV = hepatitis C virus; NR = not reported; PLAC12 = 12 weeks placebo; Peg-INF/RBV12 = 12 weeks pegylated interferon plus ribavirin; SOF12+Peg-INF/RBV12 = 12 weeks sofosbuvir + 12 weeks pegylated interferon plus ribavirin; SOF12RBV12 = 12 weeks sofosbuvir + 12 weeks ribavirin; SOF16RBV16 = 16 weeks sofosbuvir + 16 weeks ribavirin; SOF24RBV24 = 24 weeks sofosbuvir + 24 weeks ribavirin; Tx = treatment.
Source: Clinical Study Reports for FISSION,[16] VALENCE,[17] FUSION,[18] POSITRON.[19]

3.4 Exposure to Study Treatments

Mean duration of exposure to study drug was generally consistent with the treatment duration as defined in their respective protocols, and thus any differences in duration of exposure between groups was protocol-defined. Exceptions were FISSION, where Peg-INF/RBV patients received treatment for a mean ±SD of 21.3 ± 5.8 weeks, when the expected duration was 24 weeks, while sofosbuvir+ribavirin patients received treatment for 11.9 ± 1.5 weeks (expected: 12 weeks). And in VALENCE, the placebo group received therapy for 7.3 ± 3.0 weeks, when expected was 12 weeks, while the genotype 2 patients received treatment for 12.0 ± 0.2 weeks (expected: 12 weeks) and the genotype 3 patients 24.0 ± 1.0 weeks (expected: 24 weeks). The short duration of placebo treatment was likely due to the fact that the placebo group was halted early after a protocol amendment that occurred while the study was ongoing.

Otherwise, in NEUTRINO, patients were treated for a mean ± SD of 11.9 ± 1.1 weeks, and in POSITRON, patients were treated for 11.9 ± 1.3 weeks in the sofosbuvir+ribavirin group and 11.8 ± 1.6 weeks in the placebo group. All of these groups had a planned treatment duration of 12 weeks. In FUSION, the 12-week sofosbuvir+ribavirin treatment group was treated for mean ±SD of 12.2 ± 0.6 weeks and the 16-week sofosbuvir+ribavirin treatment group was treated for a mean ±SD of 16.1 ± 0.2 weeks.

3.5 Critical Appraisal

3.5.1 Internal Validity

NEUTRINO, the only trial conducted in patients with genotypes 1 and 4 that employed the Health Canada–recommended regimen of sofosbuvir was a single-arm trial that employed an external control as a comparison group to assess the primary outcome (SVR12). The use of an external control adds a significant confounder when trying to make comparisons between groups. In an RCT, a key purpose of randomization is to ensure that the two populations being compared are as similar as possible, so that by the end of the study, any differences in response between groups can be attributed solely to the interventions being compared. When an external control is used, there is no way to ensure that the populations being compared are truly similar, as the control population was enrolled at a different time, for a different purpose from that of the study drug. One notable difference between NEUTRINO patients and those in the studies used as the external control was the enrolment of non-genotype 1 patients in NEUTRINO (11% were non-genotype 1), who may be more likely than genotype 1 patients to attain SVR. The clinical expert believed that the estimate obtained from the external control of 60% is reasonable. Nevertheless, the use of an external control reduces confidence in the comparison being made. The trials from which the control responder rate of 60% was derived were conducted in treatment-naive patients with HCV genotype 1 and employed the appropriate Health Canada–approved regimens for boceprevir (SPRINT-2)[6] and telaprevir (ADVANCE).[40] In SPRINT-2 and ADVANCE, 38% and 44% of patients treated with Peg-INF/RBV for 48 weeks respectively achieved SVR. Given that NEUTRINO lacks a control group of Peg-INF/RBV -treated patients, comparisons of the response rates across the control groups of the various studies cannot be made to assist in assessing the comparability of the NEUTRINO patients to those in SPRINT-2 and ADVANCE.

Single-arm studies are also prone to considerable bias, as patients and providers are aware of their assigned intervention. Objective outcomes such as SVR are less likely to be directly affected; however, more subjective outcomes such as quality of life are at significant risk of bias if patients in the study are all aware that they are receiving the study drug. For example, a patient may report improved quality of life simply because they are taking a novel intervention. Knowledge of their intervention may also bias results indirectly by affecting adherence. Patients may be more likely to closely adhere to therapy if they are taking a novel intervention, particularly if they are anticipating that this intervention will be an

improvement over existing therapies. Improved adherence might, of course, lead to better outcomes. Knowledge of treatment assignment might also bias harms, particularly adverse events. If patients are aware that they are taking an active therapy, they might be more likely to attribute an adverse effect to a drug, or may even be more likely to report an adverse effect.

FISSION, the only RCT enrolling CHC patients with genotypes 2 and 3 that compared sofosbuvir+ribavirin with the standard of care (Peg-INF/RBV) was an open-label non-inferiority study. It is problematic that the non-inferiority study was conducted in a mixed genotype 2 and genotype 3–infected patient population, given that the comparative efficacy may be expected to differ by genotype. Combining these two genotypes in one analysis may mask clinically important differences within a genotype subgroup. While subgroup results were reported by genotype, the statistical analyses were not adequately powered for between-treatment comparisons within subgroups. Further, given that FISSION was an open-label trial, it may have been subject to reporting bias, as described above. In addition, 28% of patients in the Peg-INF/RBV group withdrew from the study, the majority due to treatment failure. According to the clinical expert, this is higher than one would expect with a Peg-INF/RBV regimen in a study of this kind. This withdrawal rate was higher than with sofosbuvir+ribavirin (13%) in FISSION, and this is largely accounted for by a much lower rate of withdrawal due to efficacy failure with sofosbuvir+ribavirin (1%). It should be noted that Peg-INF/RBV Peg-INF/RBV–treated patients in FISSION who received at least one dose of study drug and had completed all scheduled on-treatment study visits were offered open-label sofosbuvir+ribavirin for 12 weeks. The fact that the difference in withdrawals was due to efficacy failure reduces concern with such a difference, as the efficacy failures are directly tied to the primary outcome. However, the differential rate of withdrawals is expected to reduce statistical power and may lead to a conclusion of non-inferiority being drawn even if it is not true.

There was a significant amount of missing data for the various quality-of-life outcomes, particularly in the FISSION study, where data were reported only for less than half of the randomized population. This makes it very difficult to assess the impact on quality of life of sofosbuvir+ribavirin compared with Peg-INF/RBV, for example. It appears that the quality-of-life analysis was included as a protocol amendment, initiated after the study was under way. These missing data reduce confidence that the results being analyzed represent the population that was originally enrolled in the study. For example, if a disproportionate number of patients with cirrhosis were missing from the dataset, this may bias results if these patients suffer more quality of life issues. This would be particularly concerning if this disproportionate number of missing cirrhotic patients occurred in only one group.

As with FISSION, both FUSION and POSITRON suffer from the lack of statistical power to make comparisons within clinically relevant subgroups such as HCV genotype, and the VALENCE study, because of the mid-study protocol changes, is merely hypothesis-generating.

3.5.2 External Validity

With the exception of VALENCE, which did not appear to specify, all the studies in this review excluded patients with HIV coinfection. This limits the generalizability of the results, as there are a number of patients infected with both HCV and HIV, and there is evidence that HIV coinfection can accelerate progression of CHC to important complications such as cirrhosis and end-stage liver disease.

Many of the included studies focused on populations in the USA, rather than an international mix of populations, and many studies did not have Canadian sites. According to the clinical expert, the impact of the lack of Canadian sites is attenuated somewhat by the fact that American sites were well represented, as Canadian CHC patients would have more in common with American patients than with

the rest of the world. That said, the multicultural nature of the Canadian population may not be well captured in the included studies.

The FUSION study enrolled patients who were previous treatment failures. However, the inclusion criteria stated that patients had to have at least 12 weeks of therapy with pegylated interferon with or without ribavirin, and it is debatable whether this is a long enough duration of therapy to identify a patient as a treatment failure. Excepting FUSION and VALENCE, the included studies limited the percentage of patients with cirrhosis to 20%. It is not clear what these limits were based on; however, the clinical expert contracted for this review indicated that the prevalence of cirrhosis among Canadian patients presenting for treatment is approximately 25%.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (section 2.2, Table 4). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Genotypes 1 and 4

a) SVR

In NEUTRINO (Table 11), the proportion of the total patient population achieving SVR12 (91%) was statistically significantly higher than an external control of 60% ($P < 0.001$). SVR responses were highest with genotypes 4, 5, and 6 (97%), followed by genotype 1a (92%) and 1b (82%). In the overall population, the proportion of SVR12 responders in patients with cirrhosis was 80%, and without cirrhosis was 93%. These subgroup data (Table 15) must be interpreted with caution as the study was not powered to draw any conclusions from these data, and any statistical testing would be limited by concerns over multiple testing.

b) Relapse

In NEUTRINO, the percentage of patients relapsing was 9% (Table 11).

c) Mortality

There were no deaths in NEUTRINO (Table 11).

d) Health-Related Quality of Life

In NEUTRINO (Table 11), there was no comparator group, although both the SF-36-PCS and the SF-36-MCS were statistically significantly lower (worse) at end of therapy compared with baseline; mean ± SD changes from baseline were −6.5 ± 9.8 and −6.9 ± 10.6, respectively.

NEUTRINO also reported data for the CLDQ-HCV, FACIT-F, and WPAI-HepC, and all of these were statistically significantly worsened at end of therapy versus baseline. The mean ±SD reduction in the CLDQ-HCV was −0.6 ± 1.0, and for the FACIT-F was −19.8 ± 25.1. The WPAI-HepC reported a mean ±SD increase in the percentage of overall impairment of 22.1% ± 31.6 for work, and 22.0% ± 31.3 for activity. No minimally clinically important differences (MCIDs) have been established for these instruments in CHC.

e) Other Efficacy Outcomes

Liver-related morbidity was not specifically reported in the included studies.

3.6.2 Genotypes 2 and 3

a) SVR

Treatment-Naive

In FISSION (Table 12), patients treated with a combination of sofosbuvir+ribavirin for 12 weeks had a similar proportion of SVR12 responders to those treated with Peg-INF/RBV for 24 weeks (67% in each group, between-group difference of 0.3% [95% CI: –7.5%, 8.0%]), thus the criteria for non-inferiority was met, with a lower bound for the 95% CI of –7.5%, greater than the non-inferiority margin of −15%. However, superiority of sofosbuvir+ribavirin versus Peg-INF/RBV was not demonstrated.

The proportion of patients achieving SVR12 was reported for subgroups based on genotype and presence or absence of cirrhosis (Table 16). In genotype 2 patients, 97% of sofosbuvir+ribavirin patients achieved SVR12, compared with 78% of Peg-INF/RBV patients; results for genotype 3 patients were 56% versus 63% for sofosbuvir+ribavirin and Peg-INF/RBV, respectively. In patients with cirrhosis, the proportion of SVR12 responders was 47% with sofosbuvir+ribavirin and 38% with Peg-INF/RBV. In patients without cirrhosis, the proportion of SVR12 responders was 72% with sofosbuvir+ribavirin and 74% with Peg-INF/RBV. A further breakdown of subgroups by genotype is provided in Appendix 4 (Table 17). Notable among these data is that for genotype 2 patients with cirrhosis, SVR12 responses occur in 91% of patients treated with sofosbuvir+ribavirin and 62% of patients on Peg-INF/RBV, while in genotype 3 patients with cirrhosis, the SVR12 responses are 34% and 30%, respectively. All of these subgroup data must be interpreted with caution as the study was not powered to draw any conclusions from these data, and any statistical testing would be limited by concerns over multiple testing.

Previous Treatment Failures

In FUSION (Table 12), patients treated with a 16-week regimen of sofosbuvir+ribavirin had a statistically significantly higher proportion of patients with SVR12 than those treated with a shorter 12-week sofosbuvir+ribavirin regimen (73% versus 51%, difference in proportions: −22% [−34%, 10%], $P < 0.001$).

In the subgroups, the proportion of SVR12 responders in genotype 3 was 62% with the 16-week regimen and 31% with the 12-week regimen. In genotype 2, the proportion of SVR12 responders was 94% with the 16-week regimen and 86% with the 12-week regimen (Table 16). With respect to cirrhosis, the proportion of SVR12 responders in patients with cirrhosis was 66% with the 16-week regimen and 31% with the 12-week regimen, and in patients without cirrhosis, it was 76% and 61% for the 16-week and 12-week regimens, respectively. Further breakdown of subgroups by genotype is available in Table 17. Although the sample sizes were small, of the genotype 3 patients with cirrhosis, 19% who were treated for 12 weeks achieved an SVR12, while 61% of the patients treated for 16 weeks achieved SVR12. All of these subgroup data must be interpreted with caution as the study was not powered to draw any conclusions from these data, and any statistical testing would be limited by concerns over multiple testing.

Patients Unwilling to Take, Ineligible for, or Intolerant of Peginterferon

In POSITRON (Table 12), which enrolled patients ineligible for, unwilling to take, or intolerant of pegylated interferon, sofosbuvir+ribavirin patients had a statistically significantly higher proportion of patients with an SVR12 response than placebo-treated patients (78% versus 0%, difference in proportions of 77% [95% CI, 71% to 84%], $P < 0.001$).

In the subgroups, among patients treated with sofosbuvir+ribavirin, the percentage of patients achieving SVR12 responses was 93% in genotype 2 and 61% in genotype 3 patients (Table 16). With respect to cirrhosis, the proportion of SVR12 responders in patients with cirrhosis was 61% and without cirrhosis was 81%. Further details of subgroups by genotype are available in Table 17. Although the

sample sizes were small, 94% of the 17 genotype 2 patients with cirrhosis achieved SVR12, while 12% of the 14 genotype 3 patients with cirrhosis achieved SVR12. These subgroup data must be interpreted with caution as the study was not powered to draw any conclusions from these data, and any statistical testing would be limited by concerns over multiple testing.

Mixed Populations (Naive and Experienced)
VALENCE (Table 12) enrolled a mixed population, including patients who were both treatment-naive and treatment-experienced, and treated genotype 2 patients with 12 weeks of sofosbuvir+ribavirin, and genotype 3 patients with 24 weeks of sofosbuvir+ribavirin. Additionally, as described in the study design section above, there was also a placebo group, and a small group (N = 11) of genotype 3 patients who received sofosbuvir+ribavirin for 12 weeks instead of 24 weeks. In VALENCE, the proportion of patients with an SVR12 was 93% for genotype 2 patients treated for 12 weeks with sofosbuvir+ribavirin and 85% in genotype 3 patients treated for 24 weeks with sofosbuvir+ribavirin. There were no responders in the 85 patients treated with placebo, and the proportion of SVR12 responders in the genotype 3 group treated with 12 weeks of sofosbuvir+ribavirin was 27%. No statistical testing was performed.

In both genotype 2 patients (treated for 12 weeks) and genotype 3 patients (treated for 24 weeks), patients with cirrhosis were less likely to achieve SVR12 compared with those without cirrhosis; 82% versus 94%, and 68% versus 91%, respectively (see Table 16).

b) Relapse

Treatment-Naive
In FISSION (Table 12), the proportion of patients experiencing relapse was statistically significantly higher for sofosbuvir+ribavirin (30%) compared with Peg-INF/RBV (21%); relative risk (RR) 1.40 (95% CI, 1.02 to 1.93), *P* = 0.04.

Previous Treatment Failures
In FUSION (Table 12), which only enrolled patients who were prior treatment failures, the proportion of patients experiencing relapse was statistically significantly less in the 16-week sofosbuvir+ribavirin group (27%) compared with the 12-week regimen (47%); RR 1.72 (95% CI, 1.16 to 2.53), *P* = 0.006.

Patients Unwilling, Ineligible, or Intolerant of Peginterferon
In POSITRON (Table 12), which enrolled patients who were unwilling to take, ineligible for, or intolerant of pegylated interferon, the proportion of patients relapsing was 21% with sofosbuvir+ribavirin, and a placebo relapse proportion could not be calculated as there were no responders in this group.

Mixed Populations (Naive and Experienced)
In VALENCE (Table 12), which enrolled a mixed population of patients, the proportion of patients relapsing was 7% for genotype 2 patients taking 12 weeks of sofosbuvir+ribavirin, and 14% for genotype 3 patients taking 24 weeks of sofosbuvir+ribavirin.

c) Mortality
There was one death across all studies, in a sofosbuvir+ribavirin patient (cocaine/heroin overdose) in FISSION (Table 12).

d) Health-Related Quality of Life

Treatment-Naive

Results and statistical analyses for the SF-36 analysis were only reported for a fraction of the intention-to-treat (ITT) population in FISSION (~40% of patients). The mean ±SD change from baseline in the SF-36-PCS at end of therapy was +0.5 ± 8.7 in the sofosbuvir+ribavirin group and −4.3 ± 9.3 in the Peg-INF/RBV group (Table 12). For the SF-36-MCS, the mean ±SD change from baseline was −3.7 ± 11.5 and −8.1 ± 12.8 for sofosbuvir+ribavirin and Peg-INF/RBV, respectively. The MCIDs for SF-36 have not been established in CHC.

Previous Treatment Failures

In FUSION, there was no statistically significant difference between the 16-week and 12-week sofosbuvir+ribavirin regimens in either the SF-36-PCS or SF-36-MCS (Table 12). For the SF-36-PCS, the mean ±SD change from baseline to end of therapy was 0.0 ± 7.0 for the 16-week regimen and −2.2 ± 7.5 for the 12-week regimen (P = 0.14), and for the SF-36-MCS was −3.5 ± 9.9 versus −4.7 ± 11.6 (P = 0.17), respectively. FUSION was the only study to report other HRQoL instruments such as CLDQ-HCV, FACIT-F, and WPAI-HepC; there were no statistically significant between-treatment differences in changes from baseline for any of these measures. For the CLDQ-HCV, the mean change from baseline was 0.0 ± 0.9 with the 16-week regimen and −0.2 ± 0.8 with the 12-week regimen (P = 0.39), and for FACIT-F was −2.8 ± 21.8 versus −10.2 ± 22.7 (P = 0.08), respectively. The WPAI-HepC reported a mean ±SD increase in the percentage of overall impairment for work of 6.8% ± 26.2 with the 16-week regimen and 11.7% ± 24.6 with the 12-week regimen (P = 1.00), and for activity, 8.7% ± 26.1 versus 7.4% ± 27.1 for the 16-week and 12-week regimens, respectively (P = 0.66). The MCIDs for all these HRQoL instruments have not been established in CHC.

Patients Unwilling to Take, Ineligible for, or Intolerant of Peginterferon

Results and statistical analyses for the SF-36 were only reported for a fraction of patients (~70%) in POSITRON. There was no difference in SF-36-PCS or SF-36-MCS scores between sofosbuvir+ribavirin and placebo (Table 12). The mean ±SD change from baseline at end of therapy for SF-36-PCS in sofosbuvir +ribavirin patients was −1.8 ± 7.7 and in placebo was −0.5 ± 6.7 (P = 0.57), and for SF-36-MCS was −5.7 ± 12.3 and −2.1 ± 9.2 (P = 0.12), respectively. The MCIDs for SF-36 have not been established in CHC.

Mixed Populations (Naive and Experienced)

Quality-of-life outcomes were not reported for VALENCE.

e) Other Efficacy Outcomes

Liver-related morbidity was not specifically reported in the included studies.

TABLE 11: KEY EFFICACY OUTCOMES IN STUDIES OF GENOTYPES 1 AND 4

	NEUTRINO Naive G1, G4, G5, G6
SVR12	**SOF12+Peg-INF/RBV12 (N = 327)**
Patients, n/N (%)	296/327 (91)
P value	*P* < 0.001[a]
Relapse	
Patients, N (%)	28/326 (9)
P value	NR
Mortality	
Deaths, N (%)	0
HRQoL: SF-36-PCS	
Mean (SD) baseline	49.5 (10.0) (N = 315)
Mean (SD) change from baseline to EOT	−6.5 (9.8) (N = 298)
P value	*P* < 0.001[b]
HRQoL: SF-36-MCS	
Mean (SD) baseline	50.6 (10.4) (N = 315)
Mean (SD) change from baseline to EOT	−6.9 (10.6) (N = 298)
P value	*P* < 0.001[b]
CLDQ-HCV	
Mean (SD) baseline	5.4 (1.1) (N = 297
Mean (SD) change from baseline to EOT	−0.6 (1.0) (N = 289)
P value	*P* < 0.001
FACIT-F	
Mean (SD) baseline	126.1 (25.7) (N = 302)
Mean (SD) change from baseline to EOT	−19.8 (25.1) (N = 294)
P value	*P* < 0.001
WPAI-HepC	
Total % overall work impairment — mean (SD)	7.9 (17.2) (N = 172)
Mean (SD) change from baseline to EOT	22.1 (31.6) (N = 149)
P value	*P* < 0.001
WPAI-HepC	
Total % overall activity impairment — mean (SD)	14.5 (23.6) (N = 303)
Mean (SD) change from baseline to EOT	22.0 (31.3) (N = 292)
P value	*P* < 0.001

CLDQ-HCV = Chronic Liver Disease Questionnaire — Hepatitis C virus; EOT = end of therapy; FACIT-F = Functional Assessment of Chronic Illness Therapy — Fatigue; G1 = genotype 1; G4 = genotype 4; G5 = genotype 5; G6 = genotype 6; HRQoL = health-related quality of life; SD = standard deviation; SOF12+Peg-INF/RBV12 = 12 weeks sofosbuvir + 12 weeks pegylated plus ribavirin; SVR = sustained virologic response; SVR12 = sustained virologic response, 12 weeks; WPAI-Hep C = Work Productivity and Activity Impairment — Hepatitis C.

[a] *P* value based on one-sample binomial exact test, compared with external control of 60%.

[b] *P* value based on Wilcoxon signed-rank test.

Source: Clinical Study Report for NEUTRINO.[15]

TABLE 12: KEY EFFICACY OUTCOMES FOR GENOTYPES 2 AND 3

	FISSION Naive G2, 3		POSITRON INF-Intolerant, -Unwilling, -Ineligible G2, G3		FUSION Failure G2, G3		VALENCE Naive or Experienced G2, G3			
SVR12	**SOF12RBV12 N = 256**	**Peg-INF/RBV24 N = 243**	**SOF12RBV12 N = 207**	**PLAC12 N = 71**	**SOF12RBV12 N = 103**	**SOF16RBV16 N = 98**	**SOF12RBV12 G2 N = 73**	**SOF12RBV12 G3 N = 11**	**SOF24RBV24 G3 N = 250**	**PLAC12 N = 85**
Patients, n/N (%)	170/253 (67)	162/243 (67)	161/207 (78)	0/71 (0)	51/100(51)	69/95 (73)	68/73 (93)	3/11 (27)	213/250 (85)	NR[a]
Proportion difference (95% CI), *P* value	0.3% (−7.5% to 8.0%), *P* = 0.94[b]		77.3% (71.0% to 83.6%), *P* < 0.001[b]		−22.4% (−34.4% to −10.3%), *P* < 0.001[b]		NR	NR	NR	
Relapse										
N (%)	74/249 (30)	46/217 (21)	42/205 (21)	0/0	47/100 (47)	26/95 (27)	5/73 (7)	6/11 (55)	34/249 (14)	NR[a]
P value	1.40 (1.02 to 1.93), *P* = 0.04[c]		Not estimable		1.72 (1.16 to 2.53), *P* = 0.006[c]		NR	NR	NR	
mortality										
Deaths, N (%)	1	0	0	0	0	0	0	0	0	0
HRQoL: SF-36-PCS										
Mean (SD) baseline	47.3 (9.9) N = 98	49.0 (10.3) N = 97	47.0 (9.1) N = 145	44.8 (10.3) N = 51	47.7 (10.0) N = 98	47.2 (9.7) N = 94	NR	NR	NR	NR
Mean (SD) change at EOT	0.5 (8.7) N = 81	−4.3 (9.3) N = 68	−1.8 (7.7) N = 132	−0.5 (6.7) N = 48	−2.2 (7.5) N = 97	0.0 (7.0) N = 85	NR	NR	NR	NR
P value	*P* < 0.001[d]		*P* = 0.57[d]		*P* = 0.14[d]					
HRQoL: SF-36-MCS										
Mean (SD) baseline	49.5 (11.2) N = 98	49.0 (10.6) N = 97	47.4 (11.3) N = 145	44.7 (13.0) N = 51	48.3 (12.0) N = 98	50.3 (10.3) N = 94	NR	NR	NR	NR
Mean (SD) change at EOT	−3.7 (11.5) N = 81	−8.1 (12.8) N = 68	−5.7 (12.3) N = 132	−2.1 (9.2) N = 48	−4.7 (11.6) N = 97	−3.5 (9.9) N = 85	NR	NR	NR	NR
P value	*P* = 0.012[d]		*P* = 0.12[d]		*P* = 0.17[d]					
CLDQ-HCV										
Mean (SD) baseline	NR	NR	NR	NR	5.2 (1.2) N = 76	5.3 (1.0) N = 75	NR	NR	NR	NR

	FISSION Naive G2, 3		POSITRON INF-Intolerant, -Unwilling, -Ineligible G2, G3		FUSION Failure G2, G3		VALENCE Naive or Experienced G2, G3			
SVR12	**SOF12RBV12 N = 256**	**Peg-INF/RBV24 N = 243**	**SOF12RBV12 N = 207**	**PLAC12 N = 71**	**SOF12RBV12 N = 103**	**SOF16RBV16 N = 98**	**SOF12RBV12 G2 N = 73**	**SOF12RBV12 G3 N = 11**	**SOF24RBV24 G3 N = 250**	**PLAC12 N = 85**
Mean (SD) change at EOT	NR	NR	NR	NR	−0.2 (0.8) N = 74	0.0 (0.9) N = 74	NR	NR	NR	NR
P value `					*P* = 0.39					
FACIT-F										
Mean (SD) baseline	NR	NR	NR	NR	120.0 (29.5) N = 74	121.5 (26.2) N = 72	NR	NR	NR	NR
Mean (SD) change at EOT	NR	NR	NR	NR	−10.2 (22.7) N = 73	−2.8 (21.8) N = 68	NR	NR	NR	NR
P value					*P* = 0.082					
WPAI-HepC										
Total % overall work impair — mean (SD)	NR	NR	NR	NR	14.3 (25.8) N = 42	10.2 (19.4) N = 48	NR	NR	NR	NR
Mean (SD) change at EOT	NR	NR	NR	NR	11.7 (24.6) N = 38	6.8 (26.2) N = 41	NR	NR	NR	NR
P value					*P* = 1.00					
WPAI-HepC										
Total % overall activity impairment — mean (SD)	NR	NR	NR	NR	22.7 (29.8) N = 70	16.3 (21.5) N = 70	NR	NR	NR	NR
Mean (SD) change at EOT	NR	NR	NR	NR	7.4 (27.1) N = 70	8.7 (26.1) N = 69	NR	NR	NR	NR
P value					*P* = 0.66					

CDR = Common Drug Review; CI = confidence interval; CLDQ-HCV = Chronic Liver Disease Questionnaire — Hepatitis C Virus; EOT = end of therapy; FACIT-F = Functional Assessment of Chronic Illness Therapy — Fatigue; G = genotype; HRQoL = health-related quality of life; SF-36-MCS = Short-Form 36 — Mental Component Summary; NR = not reported; SF-36-PCS = Short-Form 36 — Physical Component Summary; PLAC12 = 12 weeks placebo; SD = standard deviation; SOF12RBV12 = 12 weeks sofosbuvir + 12 weeks ribavirin; SOF16RBV16 = 16 weeks sofosbuvir + 16 weeks ribavirin; SOF24RBV24 = 24 weeks sofosbuvir + 24 weeks ribavirin; SVR12 = sustained virologic response, 12 weeks; WPAI-HepC = Work Productivity and Activity Impairment — Hepatitis C.

[a]The placebo group of VALENCE was halted early; however, the manufacturer notes that there were no viral responses in the placebo group, at any time point.

[b]Difference in proportions between-treatment groups and associated 95% CI are calculated based on stratum-adjusted Mantel–Haenszel proportions.

[c]*P* value based on calculation of relative risk, performed by CDR.

[d]*P* value based on Wilcoxon rank-sum test.

Source: Clinical Study Reports for FISSION,[16] VALENCE,[17] FUSION,[18] POSITRON,[19] Zeuzem 2014 (VALENCE).[20]

3.7 Harms

Only those harms identified in the review protocol are reported below (section 2.2). For VALENCE, harms for all genotype 3 patients are reported together as one group, including the small number (N = 11) treated for 12 weeks and the post-amendment group treated for 24 weeks (N = 250).

3.7.1 Adverse Events

The proportion of sofosbuvir-treated patients experiencing at least one adverse event ranged between 86% and 96% across studies. In NEUTRINO, 95% of patients reported an adverse event (Table 13). In FISSION, 86% of sofosbuvir+ribavirin and 96% of Peg-INF/RBV patients experienced an adverse event (Table 14). In POSITRON, 89% of sofosbuvir+ribavirin and 78% of placebo patients experienced an adverse event, and in VALENCE, 86% in the 12-week and 91% in the 24-week sofosbuvir regimens, and 72% with placebo (note that placebo patients had shorter exposure in VALENCE, seven weeks, compared with the other regimens), experienced an adverse event. The proportion of patients with adverse events in FUSION was similar between the longer 16-week (88%) and shorter 12-week (89%) sofosbuvir+ribavirin regimens.

3.7.2 Serious Adverse Events

The proportion of patients experiencing a serious adverse event ranged between 1% and 5% across all studies (Table 13 and Table 14). There was no clear pattern of reporting of specific serious adverse events.

3.7.3 Withdrawals Due to Adverse Events

Study withdrawal due to an adverse event ranged between 0% and 12% across groups in the included studies, although the Peg-INF/RBV group in FISSION was the only group above 4% WDAE. In FISSION, 1% of sofosbuvir+ribavirin patients and 12% of Peg-INF/RBV patients withdrew due to an adverse event (Table 14). Note that Peg-INF/RBV patients were treated for 24 weeks, while sofosbuvir+ribavirin were treated for 12 weeks.

3.7.4 Notable Harms

The most common adverse events in the sofosbuvir+ribavirin regimens (Table 14) were fatigue (range: 23% to 47%), headache (21% to 33%), nausea (13% to 31%) and insomnia (11% to 29%). These were also the most common adverse events in the sofosbuvir+ribavirin and Peg-INF/RBV groups in FISSION (fatigue: 36% and 55%; headache: 25% and 44%; nausea: 18% and 29%; insomnia: 12% and 29%, respectively) and in the sofosbuvir+ Peg-INF/RBV group in NEUTRINO (Table 13: fatigue: 59%; headache: 36%; nausea: 34%; insomnia: 25%).

There was one sofosbuvir+ribavirin patient with neutropenia (grade 4) across all the studies, while in FISSION, 12% of Peg-INF/RBV patients experienced grade 3 neutropenia and 3% grade 4 neutropenia. Similar results were seen with sofosbuvir+ Peg-INF/RBV in NEUTRINO (grade 3: 15%; grade 4: 5%). Anemia occurred with 8% of sofosbuvir+ribavirin and 12% of Peg-INF/RBV in FISSION. In POSITRON, 13% of sofosbuvir+ribavirin had anemia, and none in placebo.

The proportion of patient with rash in FISSION was 9% with sofosbuvir+ribavirin and 18% with Peg-INF/RBV, and for pruritus, it was 7% and 17%, respectively (Table 14). In POSITRON, rash was similar between sofosbuvir+ribavirin and placebo (9% in each group) and this was also the case for pruritus (11% versus 9%, respectively). In VALENCE, rash was reported by 1% of patients in the 12-week sofosbuvir+ribavirin regimen and 9% of patients in the 24-week sofosbuvir+ribavirin regimen. Rash was

reported in 2% of placebo patients, although due to early termination of this group, they had a shorter follow-up.

Depression was reported as an AE in 6% of sofosbuvir+ribavirin and 14% of Peg-INF/RBV patients in FISSION. In POSITRON, 7% of sofosbuvir+ribavirin and 1% of placebo patients reported depression (Table 14).

TABLE 13: HARMS IN STUDIES OF GENOTYPES 1 AND 4

	NEUTRINO
Adverse Events	**SOF12+Peg-INF/RBV12 N = 327**
Total patients, n (%)	310 (95)
Specific AEs	
Fatigue	194 (59)
Headache	118 (36)
Nausea	112 (34)
Insomnia	81 (25)
Decreased appetite	58 (18)
Flu-like illness	51 (16)
Chills	54 (17)
Pyrexia	58 (18)
Pruritus	56 (17)
Anemia	69 (21)
Rash	59 (18)
Diarrhea	39 (12)
Arthralgia	−47 (14)
Dizziness	41 (13)
Depression	31 (10)
Thrombocytopenia	7 (2)
AEs of interest	
↓Neutrophils — grade 3	49 (15)
gr 4	17 (5)
Serious adverse events	
Total patients, n (%)	4 (1)
WDAE	
n (%)	5 (2)

AE = adverse event; INF = interferon; SOF12+Peg-INF/RBV12 = 12 weeks sofosbuvir + 12 weeks pegylated interferon plus ribavirin; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for NEUTRINO.[15]

TABLE 14: HARMS FOR GENOTYPES 2 AND 3

	FISSION		POSITRON		FUSION		VALENCE		
Adverse Events	**SOF12RBV12 N = 256**	**Peg-INF/RBV24 N = 243**	**SOF12RBV12 N = 207**	**PLAC12 N = 71**	**SOF12RBV12 N = 103**	**SOF16RBV16 N = 98**	**SOF12RBV12 G2 N = 73**	**SOF24RBV24 G3 N = 261**	**PLAC12 N = 85**
Total patients, n (%)	220 (86)	233 (96)	185 (89)	55 (78)	92 (89)	86 (88)	72 (86)	228 (91)[a]	61 (72)
≥ 10% difference between groups									
Fatigue	92 (36)	134 (55)	91 (44)	17 (24)	46 (45)	46 (47)	19 (23)	75 (30)	16 (19)
Headache	64 (25)	108 (44)	43 (21)	14 (20)	26 (25)	32 (33)	24 (29)	74 (30)	23 (27)
Nausea	46 (18)	70 (29)	46 (22)	13 (18)	22 (21)	20 (20)	26 (31)	32 (13)	9 (11)
Insomnia	31 (12)	70 (29)	39 (19)	3 (4)	21 (20)	28 (29)	9 (11)	41 (16)	2 (2)
Decreased appetite	17 (7)	44 (18)	7 (3)	7 (10)	9 (9)	5 (5)	5 (6)	16 (6)	4 (5)
Flu-like illness	7 (3)	44 (18)	8 (4)	2 (3)	1 (1)	3 (3)	1 (1)	16 (6)	4 (5)
Chills	7 (3)	43 (18)	7 (3)	1 (1)	2 (2)	0	0	5 (2)	0
Pyrexia	6 (2)	33 (14)	9 (4)	0	4 (4)	3 (3)	7 (8)	9 (4)	2 (2)
Pruritus	19 (7)	42 (17)	23 (11)	6 (9)	12 (12)	7 (7)	20 (24)	67 (27)	8 (9)
Anemia	20 (8)	28 (12)	27 (13)	0	11 (11)	4 (4)	6 (7)	16 (6)	1 (1)
Rash	23 (9)	43 (18)	18 (9)	6 (9)	7 (7)	12 (12)	1 (1)	23 (9)	2 (2)
Diarrhea	23 (9)	42 (17)	19 (9)	4 (6)	15 (15)	6 (6)	4 (5)	30 (12)	4 (5)
Arthralgia	15 (6)	35 (14)	16 (8)	1 (1)	11 (11)	9 (9)	3 (4)	24 (10)	6 (7)
Dizziness	27 (11)	33 (14)	19 (9)	5 (7)	6 (6)	5 (5)	5 (6)	18 (7)	2 (2)
Depression	14 (6)	34 (14)	15 (7)	1 (1)	6 (6)	6 (6)	0	1 (< 1)	0
Thrombocyto-penia	0	23 (10)	0	1 (1)	2 (2)	0	0	1 (< 1)	0
AEs of interest									
↓Neutrophils — grade 3	0	30 (12)	0	1 (1)	0	0	1 (1)	0	1 (1)
grade 4	0	6 (3)	0	0	1 (1)	0	0	0	0
Serious adverse events									
Total patients, n (%)	7 (3)	3 (1)	11 (5)	2 (3)	5 (5)	3 (3)	0	10 (4)	2 (2)
WDAE									
Total patients, n (%)	3 (1)	29 (12)	5 (2)	3 (4)	1 (1)	0	1 (1)	1 (< 1)	1 (1)

PLAC12 = 12 weeks placebo; Peg-INF/RBV12 = 12 weeks pegylated interferon plus ribavirin; SOF12RBV12 = 12 weeks sofosbuvir + 12 weeks ribavirin; SOF16RBV16 = 16 weeks sofosbuvir + 16 weeks ribavirin; SOF24RBV24 = 24 weeks sofosbuvir + 24 weeks ribavirin; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for FISSION,[16] VALENCE,[17] FUSION,[18] POSITRON.[19]
[a]For VALENCE, harms for all genotype 3 patients are reported together as one group, including the small number (N = 11) treated for 12 weeks and the post-amendment group treated for 24 weeks (N = 250).

4. DISCUSSION

4.1 Summary of Available Evidence

Five studies met the inclusion criteria for this systematic review. One study (NEUTRINO) was a single-arm study that enrolled treatment-naive patients with genotypes 1, 4, 5, and 6. The other four studies were RCTs that enrolled patients with genotypes 2 or 3 (FUSION, POSITRON, FISSION, and VALENCE). FISSION was an open-label non-inferiority RCT that compared sofosbuvir+ribavirin for 12 weeks versus Peg-INF/RBV for 24 weeks in treatment-naive patients. FUSION was a double-blind RCT that compared two durations of the combination of sofosbuvir+ribavirin (12 weeks versus 16 weeks) in patients who had failed prior treatment with Peg-INF/RBV (with or without ribavirin). POSITRON was a double-blind RCT that compared sofosbuvir+ribavirin for 12 weeks versus placebo in patients ineligible for, intolerant of, or unwilling to take interferon. VALENCE was initially designed as a double-blind RCT to compare 12 weeks of sofosbuvir+ribavirin to placebo. However, the protocol for VALENCE was changed during the study to extend the treatment duration of sofosbuvir+ribavirin from 12 to 24 weeks in genotype 3 patients, provided they had not already completed the 12-week course. The placebo group was halted, and the remaining groups were unblinded and the study became a descriptive study, with two remaining groups, both treated with sofosbuvir+ribavirin (genotype 2 had a 12-week regimen; genotype 3 had a 24-week regimen).

4.2 Interpretation of Results

4.2.1 Efficacy

The manufacturer is seeking reimbursement for sofosbuvir in four different patient populations. The first is for sofosbuvir, in combination with Peg-INF/RBV, in treatment-naive patients with CHC genotype 1. NEUTRINO was the only study that addressed this patient population using the Health Canada–recommended dosing regimen, and although the study met its primary outcome (≥ 60% of patients achieving SVR12), it was a single-arm study whose patient population had uncertain comparability with patients enrolled in the trials used to derive the external control of 60% (SPRINT-2 and ADVANCE), and this limits the conclusions that can be drawn from it. The manufacturer did conduct a phase 2 RCT of sofosbuvir+ Peg-INF/RBV response-guided therapy compared with 48 weeks of Peg-INF/RBV, the PROTON study; see APPENDIX 6: SUMMARY OF OTHER STUDIES. The sofosbuvir regimen employed in PROTON, sofosbuvir+Peg-INF/RBV for 12 weeks followed by either an additional 12 or 36 weeks of Peg-INF/RBV based on early response to treatment, is not consistent with the Health Canada–approved regimen. While the proportion of patients achieving SVR in the sofosbuvir treatment group in PROTON was 92%, which was similar to the 91% of sofosbuvir patients achieving SVR in NEUTRINO, it should be noted that 58% of the Peg-INF/RBV–treated patients in PROTON achieved SVR, which is higher than the Peg-INF/RBV–treated patients who achieved SVR in the SPRINT-2 and ADVANCE studies (38% and 44%, respectively), whose combined boceprevir and telaprevir treatment groups were used as the external control for NEUTRINO. These observations support the consideration that the trials used to derive the 60% external control for NEUTRINO may contain patients who are not comparable to those patients in the NEUTRINO trial, thus overstating any implied comparisons of efficacy between sofosbuvir and telaprevir or boceprevir. An NMA was submitted by the manufacturer, comparing the efficacy of sofosbuvir with boceprevir and telaprevir in treatment-naive patients with CHC genotype 1 based on SVR (see APPENDIX 7: SUMMARY OF COMPARATORS). The primary model, which was restricted to RCTs, found that all three DAAs were superior to Peg-INF/RBV alone, but that there were no statistically significant differences between sofosbuvir and boceprevir or between sofosbuvir and telaprevir. A secondary model, which included uncontrolled trials, did suggest sofosbuvir is superior to boceprevir and telaprevir; however, the model had many limitations that were considered to bias the results. It should be noted that CDR identified no sofosbuvir studies meeting criteria for inclusion in this

systematic review that were conducted in treatment-experienced patients with genotype 1 infection, and the manufacturer is requesting listing of sofosbuvir for treatment of CHC genotype 1 infection only in treatment-naive patients.

The manufacturer is also seeking reimbursement for sofosbuvir, in combination with ribavirin, in Peg-INF/RBV–experienced patients with genotypes 2 or 3. FUSION was the only study that focused exclusively on a patient population with genotypes 2 or 3 who had experience with interferon treatment (with or without ribavirin), and this study compared two different durations of sofosbuvir+ribavirin (12 versus 16 weeks). Thus, no study has demonstrated superiority of sofosbuvir+ribavirin versus Peg-INF/RBV in patients previously treated with Peg-INF/RBV. However, FUSION reported that a 16-week course of sofosbuvir+ribavirin resulted in a statistically significantly higher likelihood of achieving SVR12 compared with a 12-week course, in a mixed genotype 2 and 3 patient population. Subgroup data, by genotype, suggest that the benefit of the longer treatment duration is greater in patients with genotype 3; however, the study was not powered for these subgroup comparisons. The design of VALENCE makes it more of a hypothesis-generating study, and the data suggest that there may indeed be important differences in the duration of sofosbuvir+ribavirin needed to treat genotype 3, versus genotype 2, and these differences might be even more pronounced in patients who have cirrhosis. However, these hypotheses will need to be tested in a prospective double-blind RCT that is adequately powered to address them. Of note, the Health Canada–approved product monograph recommends a treatment duration of 12 weeks for patients with genotype 2; a treatment duration of 16 weeks is recommended for patients with genotype 3, with consideration to extending the duration up to 24 weeks based on potential risks and benefits for individual patients, which may include cirrhosis status and treatment history.

Finally, the manufacturer is seeking reimbursement for sofosbuvir, in combination with ribavirin, for patients infected with HCV genotypes 2 and 3 in whom interferon is medically contraindicated, and thus would not be eligible for treatment with Peg-INF/RBV, which has been the standard of care for such patients. The manufacturer considers the POSITRON study, which compares sofosbuvir+ribavirin with placebo, to be relevant to this patient population, given that POSITRON enrolled patients who were intolerant of, ineligible for, or unwilling to take pegylated interferon. Approximately 44% of patients in POSITRON were categorized as interferon ineligible (with 9% being intolerant and 47% unwilling). Product monograph contraindications to interferon include those with hypersensitivity to interferon, autoimmune hepatitis, decompensated cirrhosis, HIV, and HCV coinfected patients with a Child-Pugh score ≥ 6.[41] However, clinical practice guidelines suggest a broader patient population should not receive Peg-INF/RBV therapy, including patients with uncontrolled psychiatric conditions and other severe concurrent medical diseases.[12] It is unclear what percentage of patients infected with CHC genotypes 2 or 3 who present for treatment would be considered to have contraindications to interferon-based treatment; however, the clinical expert contracted for this review indicated this may be 15% to 20%.

What appears to be missing from the manufacturer's requested listing criteria is CHC patients with genotypes 2 or 3 who are treatment naive and are able to take pegylated interferon. This population was seen in FISSION, which enrolled patients with genotype 2 and 3 who were treatment naive. The results from FISSION suggest that a 12-week sofosbuvir+ribavirin regimen is non-inferior to, but not superior to 24 weeks of Peg-INF/RBV in a mixed population of genotype 2 and 3 patients who are treatment naive.

The more serious clinical complications of CHC, such as hepatocellular carcinoma and cirrhosis, typically take years to develop and only arise in a fraction of patients. Although mortality and morbidity were key

efficacy outcomes of this review, none of the included studies were of sufficient size or duration to assess these outcomes. However, observational evidence suggests that achievement of SVR is associated with reduced liver-related morbidity and mortality, and all-cause mortality.[42]

The impact of HCV and its treatment on quality of life was an issue highlighted by patients and caregivers in their impact statement to CDR. They noted that the symptoms of HCV and side effects of treatment can leave patients completely dependent and unable to contribute financially, physically, psychologically, or emotionally to the household and their relationships. Although quality of life was reported in all studies except VALENCE, there are limitations to the data provided, most notably the significant amount of missing data. For example, in treatment-naive patients (FISSION), no conclusions can be drawn about quality of life, as the analysis was performed only on less than 40% of the ITT population. In POSITRON, there was no statistically significant difference in quality of life versus placebo, and FUSION only compared two different treatment durations of sofosbuvir-ribavirin.
However, compared with other DAAs approved for use in CHC genotype 1, sofosbuvir has the potential advantage of a shorter overall duration of therapy, which may be expected to reduce the length of time patients would be required to suffer the effects of therapy, and potentially increase the number of patients who complete their prescribed treatment.

At present, there is no indication that resistance to sofosbuvir is an issue. In the included studies, there have thus far been no reports of resistance-associated mutations with this novel therapy. It is not clear whether this lack of resistance is a function of the novelty of the agent, a status that might change with further exposure, or whether it is a function of the drug's mechanism, or simply the shortened duration of therapy.

4.2.2 Harms

The design of the included studies did not provide an opportunity to isolate the adverse effects of sofosbuvir; therefore, it is not possible to ascertain the contribution of this first-in-class agent to the harms associated with the regimens to which it belongs. Additionally, since the duration of follow-up was relatively short (typically up to 24 weeks post-treatment), no conclusions can be drawn with respect to the long-term safety of sofosbuvir. There were no clear signals with respect to unusual harms that are not already associated with Peg-INF/RBV.

Data from FISSION suggest that fatigue, headache, nausea, and insomnia are the most common adverse events with both the sofosbuvir+ribavirin regimen and the Peg-INF/RBV regimen, although the incidence was numerically lower for each of these events with the sofosbuvir+ribavirin regimen when compared with Peg-INF/RBV. There were no reports of either grade 3 or 4 neutropenia with sofosbuvir+ribavirin in FISSION, while 12% of Peg-INF/RBV patients had grade 3 and 3% had grade 4 neutropenia. Additionally, no sofosbuvir+ribavirin patients had thrombocytopenia, while this occurred in 10% of Peg-INF/RBV patients, and anemia was reported in 8% versus 12% of sofosbuvir+ribavirin versus Peg-INF/RBV patients. Other adverse effects classically associated with pegylated interferon were also lower with sofosbuvir+ribavirin, including flu-like illness, chills, and fever.

With respect to tolerability, 1% of sofosbuvir+ribavirin and 12% of Peg-INF/RBV patients in FISSION withdrew due to an adverse event, which suggests that the pegylated interferon-free regimen may be better tolerated by patients, although it should be noted that this was an open-label trial and patients may have been biased by their prior perceptions of pegylated interferon. There was no difference in withdrawals due to adverse events between sofosbuvir+ribavirin and placebo in POSITRON or in VALENCE, again suggesting that a regimen that substitutes sofosbuvir instead of pegylated interferon

might end up being more tolerable than the traditional Peg-INF/RBV regimen. Tolerability was an important issue identified by patients in their impact statement to CDR, and they also suggested that the lack of tolerability of the Peg-INF/RBV regimen negatively affects persistence with therapy.

4.3 Other Considerations

Treatment of CHC is a therapeutic area in rapid evolution, with a number of interferon- and ribavirin-free regimens moving toward regulatory approval. Several regimens are expected to receive regulatory approval in the near future, including sofosbuvir. The COSMOS study examines regimens that combine sofosbuvir with simeprevir (with or without ribavirin). Although the sample was small, genotype 1 patients who received sofosbuvir plus simeprevir had a 100% SVR12 (N = 16) after 24 weeks of therapy. With 12 weeks of therapy, the SVR12 was 93% (N = 14).[10] These patients were either previous null responders, or treatment naive, but all had advanced cirrhosis or fibrosis. The 2014 European Association for the Study of the Liver guidelines list 12 weeks of sofosbuvir plus simeprevir as an option for genotype 1 patients, although it is option 5, with a B1 recommendation. The authors note that there does not appear to be a major advantage of adding ribavirin, unless the patient is a prior non-responder or has evidence of cirrhosis.[11,12] The 2014 American Association for the Study of Liver Diseases guidelines recommend sofosbuvir plus simeprevir (with or without ribavirin) for genotype 1 patients who are ineligible for interferon (Class I, Level B).[13] This combination has not received regulatory approval by Health Canada, but has been submitted to the FDA, according to a recent press release.[14]

5. CONCLUSIONS

There were four RCTs included in this review that enrolled patients with genotypes 2 or 3 (FISSION, FUSION, POSITRON, VALENCE), but only one single-arm study (NEUTRINO) that included patients with genotypes 1 or 4. The genotype 2 and 3 studies featured a variety of populations and interventions, and with respect to SVR12 responses, the combination of 12 weeks of sofosbuvir+ribavirin demonstrated non-inferiority to 24 weeks of Peg-INF/RBV in a treatment-naive population (FISSION), and superiority to placebo in a population that was ineligible for, intolerant of, or unwilling to take pegylated interferon (POSITRON). Subgroup data from FUSION and findings from the descriptive VALENCE study suggest that genotype 3 patients may benefit from a longer duration of sofosbuvir+ribavirin (up to 24 weeks), compared with genotype 2 patients (12 weeks); however, due to design limitations, these findings are hypothesis-generating only. The shorter and potentially more tolerable sofosbuvir+ribavirin regimen might be expected to provide relatively better quality of life compared with Peg-INF/RBV, but there was no evidence of this from the included studies, in part due to a considerable amount of missing data for this outcome, which rendered questionable results.

NEUTRINO lacked a control group, but sofosbuvir+Peg-INF/RBV was demonstrated to be superior, in terms of SVR, to an external control of 60% in a treatment-naive, primarily genotype 1 and 4 population. CDR identified no studies of sofosbuvir in treatment-experienced CHC genotype 1 patients that met the criteria for inclusion in this systematic review.

Across all studies, there were no novel safety or tolerability issues that could be attributed to the addition of sofosbuvir to either ribavirin or Peg-INF/RBV. When compared with Peg-INF/RBV, sofosbuvir+ribavirin appeared to be more tolerable, as measured by withdrawals due to adverse events.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by Common Drug Review staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Five patient groups representing people with the hepatitis C virus (HCV) provided input.

The Canadian Liver Foundation (CLF) is a national organization committed to reducing the incidence and impact of liver disease for Canadians living with or at risk of liver disease, through research, public and professional education programs, patient support programs, and other fundraising and outreach efforts. The CLF has received unrestricted educational grants from Gilead Sciences Canada Inc., and other pharmaceutical companies. The Chairman of CLF has received honoraria from pharmaceutical companies, including Gilead Sciences Canada Inc.

Le Centre Associatif Polyvalent d'Aide Hépatite C (CAPAHC) is a Quebec organization whose mission is to provide support to people infected with, or affected by, hepatitis C, and/or coinfected with HIV, and to promote general health and well-being through prevention and knowledge acquisition regarding these and related diseases by means of educational awareness programs. Membership includes active members (patients) and supporting members (volunteers, and people with loved ones suffering from the disease).

CAPAHC has received financial support from AbbVie, Gilead, Merck, Roche, and Vertex and declared no conflicts of interest in the preparation of this submission.

Canadian Treatment Action Council (CTAC) is a national non-governmental organization run by and for people living with HIV, including those who are coinfected with HCV and hepatitis C. CTAC addresses policy and program issues related to access to treatment, care, and support for people living with HIV or hepatitis C. Full membership is limited to persons living with HIV or organizations with a substantial HIV mandate. CTAC has received unrestricted educational grants from Gilead Sciences Canada Inc. and other pharmaceutical companies. CTAC declared no conflicts of interest in the preparation of this submission.

HepCBC — the Hepatitis C Education and Prevention Society (HepCBC) is a non-profit organization run by and for people affected by HCV in British Columbia. HepCBC focuses on providing peer support groups, anti-stigma activities, and prevention education, and encouraging testing among at-risk groups. HepCBC received funding from pharmaceutical companies including Gilead Sciences Canada Inc., to support its educational activities, and the author of the submission received funding to attend conferences.

The Pacific Hepatitis C Network's mission is to strengthen the capacity of individuals and organizations throughout British Columbia to prevent HCV infections and improve the health and treatment outcomes of people with HCV. Its members include individuals at risk, exposed to, or concerned about HCV. Pacific Hepatitis C Network received no financial support from pharmaceutical industry. No conflicts of interest were declared.

2. Condition and Current Therapy-Related Information

This information was collected through online surveys or interviews with Canadian patients, caregivers, and health care professionals, direct contact with patients, expert opinion, and printed sources.
HCV is a serious and potentially life-threatening liver disease that is contracted through blood-to-blood contact with an infected person. The virus attacks the liver, leading to fibrosis, cirrhosis, liver cancer, liver failure, and even death.

Patients may live with HCV for years with few symptoms, but must cope with the stigma associated with HCV and are often reluctant to disclose their HCV status for fear of rejection, discrimination, or ostracism. The social stigma, fear of spreading the infection, and the uncertainty regarding their future health exact a high emotional toll on patients that may lead to depression, anxiety, and social isolation.

Debilitating physical symptoms may develop, such as chronic fatigue (highlighted in all submissions), mental confusion, memory loss, and mood swings that can result in job loss and relying on disability benefits or social assistance. Other debilitating symptoms include insomnia, muscle or joint pain, nausea, headaches, abdominal discomfort, itchy skin, hair loss, and food sensitivities. Patients with advanced disease develop severe symptoms and complications, such as retaining fluid in their abdomens and legs, confusion due to build-up of toxins, and life-threatening bleeding from esophageal varices. For some, the physical and financial impact of HCV may increase their vulnerability to living in poor or unstable housing with few social supports. The symptoms of hepatitis C also affect personal relationships, resulting in increasing isolation and depression. Patients are often too tired to complete basic household tasks, and cannot participate in family and community activities.

Spouses and loved ones who care for patients with HCV are faced with a substantial burden, as the symptoms of HCV and side effects of treatment can leave the patient completely dependent and unable to contribute financially, physically, psychologically, or emotionally to the household, the relationship, or the care of children. Caregivers must endure their loved one's mood swings, dietary problems, and lack of energy and concentration while they shoulder the responsibility for managing doctor's appointments, drug regimens, and household responsibilities. As the patient's symptoms and behaviour become more difficult to manage, families and marriages can break apart due to stress, financial difficulties, and social isolation.

Current therapy is 24 to 48 weeks of dual therapy (pegylated interferon plus ribavirin). In genotype 1 HCV, boceprevir or telaprevir may be added to pegylated interferon plus ribavirin, becoming triple therapy. Dual therapy involves weekly injections of pegylated interferon plus six to eight ribavirin pills per day. Its adverse effects can be severe and debilitating, affecting patients' work, families, and mental health. Its side effects include anemia, susceptibility to infection, sleep loss, depression, mood swings, flu-like illness, rashes, taste disturbances, hair loss, headaches, weakness, nausea, severe fatigue, and weight loss. The addition of boceprevir and telaprevir has increased the cure rates to approximately 75% for some patient groups; however, rates are lower for patients who failed previous therapy. Their addition increases the risk of adverse events, particularly rash and anemia; increases the pill burden by six to 12 pills per day; and increases the risk of drug interactions. Many patients cannot tolerate treatment and are either never treated or stop therapy early. Those who fail therapy have few treatment options. Access to treatment is a major roadblock and many patients who do not meet eligibility criteria are denied treatment through provincial drug plans, or must wait for treatment until they show serious liver damage.

3. Related Information About the Drug Being Reviewed

None of the respondents had treatment experience with sofosbuvir.

Patients believe sofosbuvir addresses a large gap and unmet patient need. It offers advantages due to its shorter treatment duration (12 to 24 weeks), easier administration (oral, once-daily dosing), decreased side effects compared with boceprevir and telaprevir, an interferon-free option for genotypes 2 and 3, and effectiveness in patients who have failed or who have relapsed on standard treatment. Patients want access to affordable treatments with tolerable side effects that cure the disease in patients with all genotypes. Many patients are waiting for new interferon-free or ribavirin-free therapies that avoid the debilitating adverse events associated with these agents.

4. Additional Information

One patient group raised concerns that access delays may occur for people living with HIV and HCV coinfection due to the lack of completed phase 3 clinical trials in this population. The group suggested that the Canadian Drug Expert Committee (CDEC) consider interim data on sofosbuvir in the coinfected population. In addition, the same group mentioned that clinical trials are currently under way that combine sofosbuvir with new therapies, and that CDEC should not limit its review to combinations already studied in phase 3 clinical trials.

Limiting treatment to patients with more advanced liver disease delays access to therapy, decreases the likelihood of a successful response to treatment, and increases the risk of liver cancer. Treatment should be initiated as early as possible and there should be no restrictions on access except those dictated by a patient's medical condition.

APPENDIX 2: LITERATURE SEARCH STRATEGY

See section 2.2: Methods for more details on literature search methods.

Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 10, 2014
Alerts:	Weekly search updates until project completion
Study Types:	No study design filters used
Limits:	Date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.nm	Name of Substance Word
.ot	Original title
.pt	Publication type
.rn	CAS registry number
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY	
#	**Searches**
1	*sofosbuvir/
2	(Sovaldi* or sofosbuvir* or GI 7977 or GI7977 or GS-7977 or GS7977 or PSI 7977 or PSI7977).ti,ab.
3	or/1-2
4	3 not conference abstract.pt.
5	4 use oemezd
6	(Sovaldi* or sofosbuvir* or GI 7977 or GI7977 or GS-7977 or GS7977 or PSI 7977 or PSI7977).ti,ab,ot,sh,hw,rn,nm.
7	(1190307-88-0 or WJ6CA3ZU8B).rn,nm.
8	or/6-7
9	8 use pmez
10	5 or 9
11	remove duplicates from 10

OTHER DATABASES	
PubMed	Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Date of Search:	March 2014
Keywords:	Hepatitis C, sofosbuvir and Sovaldi
Limits:	No date limit, English only

Relevant websites from the following sections of the Canadian Agency for Drugs and Technologies in Health grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials
- Databases (free).

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Kowdley KV, Lawitz E, Crespo I, Hassanein T, Davis MN, DeMicco M, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. Lancet. 2013 Jun 15;381(9883):2100-7.	Irrelevant comparator
Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med. 2013 Jan 3;368(1):34-44.	Irrelevant regimen
Lawitz EJ, Rodriguez-Torres M, Denning J, Mathias A, Mo H, Gao B, et al. All-oral therapy with nucleotide inhibitors sofosbuvir and GS-0938 for 14 days in treatment-naive genotype 1 hepatitis C (nuclear). J Viral Hepat. 2013 Oct;20(10):699-707.	Irrelevant regimen
Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014 Feb 8;383(9916):515-23.	Irrelevant regimen
Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. Lancet Infect Dis. 2013 May;13(5):401-8.	Irrelevant regimen
Final clinical study report: P7977-0422 (PROTON). A multi-center, placebo-controlled, dose ranging study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics following oral administration of PSI-7977 in combination with pegylated interferon and ribavirin in treatment-naive patients with chronic HCV infection genotype 1, and an open label assessment of PSI-7977 in patients with HCV genotypes 2 or 3 [**CONFIDENTIAL** internal manufacturer's report]. Foster City (CA): Gilead Sciences, Inc.; 2012 Aug 28.	Irrelevant regimen
Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology. 2014 Mar;146(3):736-43.	Irrelevant regimen
Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014 Jan 16;370(3):211-21.	Irrelevant regimen
Rodriguez-Torres M, Lawitz E, Kowdley KV, Nelson DR, DeJesus E, McHutchison JG, et al. Sofosbuvir (GS-7977) plus peginterferon+ribavirin in treatment-naive patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial. J Hepatol. 2013 Apr;58(4):663-8.	Inappropriate study design
Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013 Aug 28;310(8):804-11.	Inappropriate regimen
Ferguson MC. Sofosbuvir with ribavirin is safe and effective in hepatitis C genotype 1 with unfavourable pretreatment characteristics. Evid Based Med. 2013 Dec 12.	Other (commentary)

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 15: SUBGROUPS: IN STUDIES OF GENOTYPES 1 AND 4, PROPORTION OF PATIENTS ACHIEVING SVR12

	NEUTRINO Naive G1, 4, 5, 6
	SOF12+Peg-INF/RBV12 N = 327
Genotype 1	1a: 206/225 (92) 1b: 54/66 (82)
Genotype 2	NA
Genotype 3	NA
Genotypes 4, 5, 6	34/35 (97)
Cirrhosis: Yes	43/54 (80)
Cirrhosis: No	253/273 (93)
INF-ineligible	NA
INF-intolerant	NA
INF-unwilling	NA
Prior treatment: non-response[a]	NA
Relapse or breakthrough[b]	NA
IL28B-CC	94/95 (99)
Non-CC	202/232 (87)

HCV = hepatitis C virus; INF = interferon; NA = not applicable; SOF12+Peg-INF/RBV12 = 12 weeks sofosbuvir + 12 weeks pegylated interferon plus ribavirin; SVR12 = sustained virologic response, 12 weeks.
[a]Non-response: Patient did not achieve undetectable HCV. RNA levels on treatment.
[b]Relapse or breakthrough: Patient achieved undetectable HCV. RNA during treatment or within 4 weeks after treatment.

TABLE 16: SUBGROUPS IN GENOTYPES 2 AND 3 — PROPORTION OF PATIENTS ACHIEVING SVR12

	FISSION Naive G2, G3			POSITRON INF-Intolerant, -Unwilling, -Ineligible G2, G3		FUSION Failure G2, G3			VALENCE Naive or Experienced G2, G3			
	SOF12RBV12 N = 256	Peg-INF/RBV24 N = 243	Difference in Proportions (95% CI)	SOF12RBV12 N = 207	PLAC12 N = 71	SOF12RBV12 N = 103	SOF16RBV16 N = 98	Difference in Proportions (95% CI)	SOF12RBV12 G2 N = 73	SOF12RBV12 G3 N = 11	SOF24RBV24 G3 N = 250	PLA N = 85
G 1	NA	NA		NA	NA	NA	NA		NA	NA	NA	NA
G2 (%)	68/70 (97)	52/67 (78)	19.5 (8.4, 31.5)	101/109 (93)	0/34	31/36 (86)	30/32 (94)	−7.6 (−24.1 to 8.5)	NA	NA	NA	NA
G3 (%)	102/183 (56)	110/176 (63)	−6.8 (−17.1 to 3.5)	60/98 (61)	0/37	20/64 (31)	39/63 (62)	−30.7 (-46.7 to −13.0)	NA	NA	NA	NA
G4, G5, G6	NA	NA		NA	NA	NA	NA		NA	NA	NA	NA
Cirrhosis: Yes (%)	23/49 (47)	19/50 (38)	8.9 (−11.0 to 28.3)	19/31 (61)	0/13	11/36 (31)	21/32 (66)	−35.1 (−56.0 to −8.6]	9/11 (82)	NR	41/60 (68)	NR
Cirrhosis: No (%)	147/204 (72)	143/193 (74)	−2.0 (−10.8 to 6.8)	142/176 (81)	0/58	39/64 (61)	48/63 (76)	−13.7 (−29.5 to 2.7)	59/63 (94)	NR	172/190 (91)	NR
INF-ineligible (%)	NA	NA		69/88 (78)	0/33	NA	NA		NA	NA	NA	NA
INF-intolerant (%)	NA	NA		13/17 (77)	0/8	NA	NA		NA	NA	NA	NA
INF-unwilling (%)	NA	NA		79/102 (78)	0/30	NA	NA		NA	NA	NA	NA
Prior Tx non-response[a] (%)	NA	NA		NA	NA	11/25 (44)	16/25 (64)	−20.0 (−46.6 to 8.9)				
Relapse/ breakthrough (%)	NA	NA		NA	NA	40/75 (53)	53/70 (76)	−22.4 (−37.4 to −6.7)				
IL28B-CC (%)	74/106 (70)	82/106 (77)	−7.5 (−19.5 to 4.4)	74/97 (76)	0/29	16/30 (53)	19/27 (70)	−17.0 (−42.2 to 8.9)	24/24 (100)	2/4 (50)	75/86 (87)	0
Non-CC (%)	96/145 (66)	79/136 (58)	8.1 (−3.5 to 19.5)	87/110 (79)	0/42	35/70 (50)	50/68 (74)	−23.5 (−39.0, to −6.4)	44/49 (90)	1/7 (14)	135/164 (82)	0

	FISSION Naive G2, G3			POSITRON INF-Intolerant, -Unwilling, -Ineligible G2, G3		FUSION Failure G2, G3			VALENCE Naive or Experienced G2, G3			
	SOF12RBV12 N = 256	Peg-INF/RBV24 N = 243	Difference in Proportions (95% CI)	SOF12RBV12 N = 207	PLAC12 N = 71	SOF12RBV12 N = 103	SOF16RBV16 N = 98	Difference in Proportions (95% CI)	SOF12RBV12 G2 N = 73	SOF12RBV12 G3 N = 11	SOF24RBV24 G3 N = 250	PLA N = 85
Tx-naïve (%)	NA	NA		NA	NA	NA	NA		31/32 (97)	0/2	98/105 (93)	0
Tx-experienced (%)	NA	NA		NA	NA	NA	NA		37/41 (90)	3/9 (33)	112/145 (77)	0
Tx-naive and cirrhotic (%)	NA	NA		NA	NA	NA	NA		2/2 (100)	0/0	12/13 (92)	0
Tx-naive and non-cirrhotic (%)	NA	NA		NA	NA	NA	NA		29/30 (97)	0/2	86/92 (94)	0
Tx-experienced and cirrhotic (%)	NA	NA		NA	NA	NA	NA		7/8 (88)	0/2	27/45 (60)	0
Tx-experienced and non-cirrhotic (%)	NA	NA		NA	NA	NA	NA		30/33 (91)	3/7 (43)	85/100 (85)	0

CI = confidence interval; G1 = genotype 1; G2 = genotype 2; G3 = genotype 3; G4 = genotype 4; G5 = genotype 5; G6 = genotype 6; HCV = hepatitis C virus; NA = not applicable; PLAC12 = 12 weeks placebo; Peg-INF/RBV12 = 12 weeks pegylated interferon + ribavirin; SOF12RBV12 = 12 weeks sofosbuvir + 12 weeks ribavirin; SOF16RBV16 = 16 weeks sofosbuvir + 16 weeks ribavirin; SOF24RBV24 = 24 weeks sofosbuvir + 24 weeks ribavirin; SVR12 = sustained virologic response, 12 weeks; Tx = treatment.

[a]Non-response: Patient did not achieve undetectable HCV RNA levels on treatment.

[b]Relapse or breakthrough: Patient achieved undetectable HCV RNA during treatment or within 4 weeks after treatment.

Source: Clinical Study Reports for FISSION,[16] VALENCE,[17] FUSION,[18] POSITRON,[19] Zeuzem 2014 (VALENCE).[20]

TABLE 17: SUBGROUPS BY GENOTYPE, GENOTYPES 2 AND 3 — PROPORTION OF PATIENTS ACHIEVING SVR12

		FISSION Naive G2, G3		POSITRON		FUSION	
		SOF12RBV12 N = 256	Peg-INF/RBV24 N = 243	SOF12RBV12 N = 207	PLAC12 N = 71	SOF12RBV12 N = 103	SOF16RBV16 N = 98
G2	Cirrhosis: Yes	10/11 (91)	8/13 (62)	16/17 (94)	0	6/10 (60)	7/9 (78)
	Cirrhosis: No	58/59 (98)	44/54 (82)	85/92 (92)	0	25/26 (96)	23/23 (100)
G3	Cirrhosis: Yes	13/38 (34)	11/37 (30)	3/14 (12)	0	5/26 (19)	14/23 (61)
	Cirrhosis: No	89/145 (61)	99/139 (71)	57/84 (68)	0	14/38 (37)	25/40 (63)
G2	IL28B-CC	31/31 (100)	28/34 (82)	40/45 (89)	0	6/7 (86)	9/11 (82)
	- CT	37/39 (95)	24/33 (73)	49/50 (98)	0	25/29 (86)	21/21 (100)
	- TT			12/14 (86)	0		
G3	IL28B-CC	43/75 (57)	54/72 (75)	34/52 (65)	0	9/23 (39)	10/16 (63)
	- CT	59/106 (56)	55/103 (53)	21/34 (62)	0	10/41 (24)	29/47 (62)
	- TT			5/12 (42)	0		
G2	INF-ineligible	NA	NA	36/41 (88)	0	NA	NA
	INF-intolerant	NA	NA	9/9 (100)	0	NA	NA
	INF-unwilling	NA	NA	56/59 (95)	0	NA	NA
G3	INF-ineligible	NA	NA	33/47 (70)	0	NA	NA
	INF-intolerant	NA	NA	4/8 (50)	0	NA	NA
	INF-unwilling	NA	NA	23/43 (54)	0	NA	NA
G2	Non-response	NA	NA	NA	NA	7/10 (70)	7/8 (88)
	Relapse or breakthrough	NA	NA	NA	NA	24/26 (92)	23/24 (96)
	Intolerant	NA	NA	NA	NA	NA	NA
G3	Non-response	NA	NA	NA	NA	4/15 (27)	9/17 (53)
	Relapse or breakthrough	NA	NA	NA	NA	15/49 (31)	30/46 (65)
	Intolerant	NA	NA	NA	NA	NA	NA

G1 = genotype 1; G2 = genotype 2; G3 = genotype 3; INF = interferon; NA = not applicable; PLAC12 = 12 weeks placebo; Peg-INF/RBV24 = 24 weeks pegylated interferon + ribavirin; SOF12RBV12 = 12 weeks sofosbuvir + 12 weeks ribavirin; SOF16RBV16 = 16 weeks sofosbuvir + 16 weeks ribavirin; SOF24RBV24 = 24 weeks sofosbuvir + 24 weeks ribavirin; SVR12 = sustained virologic response, 12 weeks.

Note that no analysis of subgroups by genotype was reported for NEUTRINO, and in VALENCE, groups were already randomized by genotype.

Source: Clinical Study Reports for FISSION,[16] VALENCE,[17] FUSION,[18] POSITRON.[19]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

A. Objectives

1) To review the validity of sustained virologic response at 12 weeks (SVR12) as a surrogate for SVR at 24 weeks (SVR24)
2) To summarize the characteristics of the following health-related quality of life instruments:
   - Chronic Liver Disease Questionnaire — Hepatitis C (CLDQ-HCV)
   - Functional Assessment of Chronic Illness Therapy — Fatigue (FACIT-F)
   - Short-Form 36 items (SF-36)
   - Work Productivity and Activity Impairment — Hepatitis C (WPAI-HepC).

B. Findings

Part 1: Validity of Sustained Virologic Response at 12 Weeks

SVR24 is the standard primary end point for assessing response to agents that treat chronic hepatitis C (CHC).[43] However, SVR12 is an emerging outcome of interest, potentially providing a means for determining treatment response earlier in either randomized controlled trials or the clinic. In 2013, the FDA published a paper in the journal *Gastroenterology* that sought to determine the predictive value of SVR12 as a surrogate for SVR24.[43] The authors reviewed data submitted to the FDA (2002-2011) from 15 phase 2 and 3 studies that included various treatment durations of pegylated interferon (peginterferon) alpha-2a, pegylated interferon alpha-2b, albinterferon alpha-2b, telaprevir, and boceprevir. The majority of the 13,599 participants were genotype 1 (N = 11,730), while genotype 2 (N = 783) and genotype 3 (N = 995) made up most of the remainder. In addition to assessing SVR12, the authors also reviewed the predictive value of SVR4 with respect to SVR24.

SVR12 was achieved by 51.8% (7,051 of 13,599 patients) and SVR24 by 50.6% (6,881 of 13,599 patients) of adults in the database. The positive predictive value between SVR12 and SVR24 was 98.3% and the negative predictive value (patients who had detectable virus at week 12 but achieved SVR24) was 98.8%. Thus, 1.2% of patients would be falsely identified as having a detectable virus if an outcome of SVR12 was adopted over SVR24, and 1.7% of patients would be falsely identified as having a sustained undetectable viral load. The authors attributed the latter case to relapse, reinfection, or "other" reasons. Results were consistent across the 15 studies, with between 0% and 4.3% of patients achieving SVR12 but not SVR24. Older studies that used HCV RNA assays with higher values for lower limits of detection had lower positive predictive values than those studies with newer, more sensitive assays. Overall, the authors concluded that SVR12 would be an appropriate primary end point for trials used by regulatory bodies to evaluate CHC treatments.

A study published in 2010 also evaluated the relevance of SVR12 as a primary outcome.[44] This study included 781 patients with CHC; all had received pegylated interferon+ribavirin. Of the 781 patients, 573 had an end-of-treatment response and were thus included in the analysis. Of the 409 patients who had an SVR12, 408 went on to have an SVR24. Therefore, this study also demonstrated a high concordance between achievement of SVR12 and eventual achievement of SVR24. The authors concluded that SVR12 is as informative as SVR24 when assessing SVR. This study used the transcription-mediated amplification assay, which is a newer, more sensitive assay.

Part 2: Health-Related Quality of Life Instruments

a) Chronic Liver Disease Questionnaire — Hepatitis C

The CLDQ is a health-related quality of life (HRQoL) instrument for patients with chronic liver disease. CLDQ includes 29 items divided into six domains: Abdominal Symptoms, Fatigue, Systemic Symptoms, Activity, Emotional Function, and Worry. For each item, the patient assigns a score of 1 (all the time) to 7 (none of the time). The domain score is divided by the number of items in the domain. Domain scores are presented on a 1 to 7 scale.[38] In this paper, the investigators stated that a change of 0.5 on the 1 to 7 scale would signify an important difference in questionnaire score; however, there is no proof of validation of this minimally clinically important difference (MCID).[38]

It appears that the CLDQ was subsequently amended for use in CHC patients. From abstracts, we could find that scores are based on a Likert scale from 0 (worst) to 7 (best) and measure Activity/Energy, Emotion, Worry, Systemic, and CLDQ-HCV Total score.[45,46] No detailed information is available.

Three abstracts on convergent validity and one abstract on construct validity of CLDQ-HCV were identified.[45-48]

Convergent Validity

- CLDQ-HCV was validated against the Fatigue Severity Scale (high score = more fatigue) in 100 consecutive healthy blood donors and from 50 CHC patients.[47] Correlations between Fatigue Severity Scale and CLDQ-HCV in the 100 healthy blood donors were as follows: Activity/ Energy, r = –0.65 (P = 0.0001); Emotion, r = –0.61 (P < 0.0001); Worry, r = –0.23 (P < 0.0001); Systemic, r = –0.39, (P < 0.0001); and Overall Score, r = 0.58 (P < 0.0001). Comparison of CLDQ-HCV scores between blood donor patients and CHC patients showed statistically significant differences in HRQoL measured by Worry (P < 0.0001), Emotion (P = 0.048), and Overall Score (P = 0.004), with worse (lower) scores in CHC patients.[47]
- CLDQ-HCV was validated against SF-36 in 50 hepatitis C patients. CLDQ-HCV Activity/Energy (A/E) domain and SF-36 vitality (VT) and physical functioning (PF) scales were used. Statistically significant correlations were shown (VT versus A/E, r = 0.84 (P < 0.0001); VT versus PF, r = 0.48, P < 0.0001)].[48]
- In another abstract, CLDQ-HCV was validated against SF-36 in 63 hepatitis C patients. The following r values were obtained (Table 18).[46] All findings were statistically significant.

TABLE 18: CORRELATION BETWEEN VARIOUS DOMAINS OF CLDQ-HCV AND SF-36

r Value (*P* Value)	CLDQ-HCV				
SF-36	Activity/Energy	Emotion	Worry	Systemic	Overall Score
Physical function	0.47 (< 0.001)	NR	NR	0.40 (0.006)	NR
Role physical	0.42 (0.001)	NR	NR	NR	NR
Bodily pain	0.47 (< 0.001)	NR	NR	0.53 (< 0.001)	0.41 (0.002)
General health	0.40 (0.003)	0.44 (0.001)	NR	0.44 (0.001)	0.41 (0.003)
Vitality	0.78 (0.001)	0.41 (0.003)	NR	0.46 (0.001)	0.57(< 0.001)
Social function	0.43 (0.001)	NR	NR	NR	NR
Role emotional	NR	NR	NR	NR	NR
Mental health	NR	0.58 (< 0.001)	NR	NR	NR
Mental component score	0.49 (0.001)	0.59 (< 0.001)	NR	0.40 (0.01)	0.49 (< 0.001)
Physical component score	0.68 (< 0.001)	NR	NR	0.52 (< 0.001)	0.44 (0.002)

CLDQ-HCV = Chronic Liver Disease Questionnaire — Hepatitis C Virus; NR = not reported; SF-36 = Short-Form 36.
Source: Escheik et al.[46]

Construct Validity

- One abstract presented the results of validation of CLDQ in 62 hepatitis C patients versus 100 healthy blood donors.[45] Hepatitis C patients received pegylated interferon with ribavirin treatment. Hepatitis C patients had lower (worse) CLDQ-HCV Overall Score at baseline compared with healthy controls (5.7 ± 0.7 versus 6.2 ± 0.5, $P < 0.0001$). Lower scores were also reported at baseline for Emotion and Worry in hepatitis C patients (5.6 ± 0.4 and 5.7 ± 0.9) compared with healthy controls (5.9 ± 0.4 and 6.9 ± 0.2), respectively. After 4 weeks and 24 weeks of treatment, Overall Scores decreased (worsened) in hepatitis C patients (5.4 ± 0.9 and 5.7 ± 0.8), and increased after treatment discontinuation (6.3 ± 0.6). The CLDQ was able to differentiate between hepatitis C patients and healthy controls. The instrument was also sensitive to change over time.[45]

An MCID for CLDQ-HCV has not been identified in hepatitis C, although one abstract[45] cited an MCID of 0.5, perhaps in reference to the paper by Younossi et al.[38] mentioned above.

b) Functional Assessment of Chronic Illness Therapy — Fatigue

The Functional Assessment of Cancer Therapy (FACT) was originally developed and validated in cancer patients.[49] The Functional Assessment of Chronic Illness Therapy (FACIT) was later derived from FACT and validated in patients with chronic illness conditions such as multiple sclerosis and rheumatoid arthritis.[50] It includes 27 items (400 questions) divided into four primary domains: physical, social/family, emotional, and functional well-being.[50] The FACIT-Fatigue scale (FACIT-F) is a 40-item scale assessing fatigue and its impact on daily activities. Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale, make up the total score, ranging from 0 (worst) to 160 (best).[29] No information on the validity of FACIT-F and MCID in hepatitis C patients was found.

c) Short-Form 36 Items

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions (GH), and role limitations due to physical and emotional problems. SF-36 also provides two component summaries: the physical component summary (SF-36-PCS) and the mental component summary (SF-36-MCS). The SF-36-PCS and SF-36-MCS and eight dimensions are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of SF-36, a change of 10 points in each dimension or 5 points in each component summary indicates a clinically meaningful improvement as determined by the patient.

A systematic review was conducted to identify and provide information on HRQoL instruments for hepatitis C.[51] The authors identified 32 studies and presented the results by types of clinical anchors (for example, hepatitis C status or liver disease severity anchors), but it was not clear in the publication which instruments contributed to the data. Nonetheless, from the publication, two results attributed to SF-36 could be extracted:

- A total of 15 studies with SF-36 were included that compared HRQoL in patients with compensated hepatitis C seropositivity versus healthy controls. All 15 studies provided cross-sectional group mean HRQoL differences stratified by hepatitis C status (the clinical anchor). Patients with hepatitis C scored lower on the various domains compared with healthy patients. The largest impact of the disease was on role physical, role emotional, and general health (Table 19).[51]
- A panel of expert was convened to indirectly estimate the MCID in hepatitis C based upon existing HRQoL data.[51] The panel consisted of three hepatologists and two HRQoL methodologists with expertise in chronic liver disease–specific HRQoL. Based on the results of the systematic review,

the panel determined that the SF-36 vitality scale captures the HRQoL domain that is most relevant to patients with hepatitis C. Using a modified Delphi technique, the expert panel generated a mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale, with a corresponding effect size of 0.2 (range 0.15 to 0.25).[51] MCIDs for other dimensions or for the two component scores were not estimated and were not found in the literature.

TABLE 19: HEPATITIS C PATIENT VERSUS HEALTHY CONTROL WEIGHTED MEAN AND MEDIAN CROSS-SECTIONAL DIFFERENCE (15 STUDIES)

Scale	Weighted Mean	Median
Physical function	−7.0	−9.3
Role physical	−15.8	−20.5
Bodily pain	−9.0	−13.7
General health	−12.6	−19.6
Vitality	−10.1	−14.4
Social function	−11.9	−10.0
Role emotional	−13.0	−12.5
Mental health	−7.2	−10.0
Mental component score	−12.8	−7.0
Physical component score	−9.1	−6.6

d) Work Productivity and Activity Impairment — Hepatitis C

The Work Productivity and Activity Impairment (WPAI) questionnaire is an instrument used to measure the impact of a disease on work and on daily activities.[39] The questionnaire elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing work was challenging, and the extent to which the patient was limited at work (work impairment) during the past seven days. A work productivity score is measured by multiplying percentages of work hours actually worked and productivity while at work. A parallel set of questions assesses activity impairment. The activity impairment domain is the impairment in daily activities other than work (for example, work around the house). Higher scores indicate better work productivity and activity performance.[39]

One study, available only as an abstract, measured the content validity of WPAI in hepatitis C using cognitive debriefing interviews. A total of seven patients interviewed confirmed that the questionnaire was relevant, understandable, and easy to complete.[52]

An MCID for WPAI has not been identified in hepatitis C.

C. Summary

A 2013 review of CHC published by authors from the FDA included 15 phase 2 and 3 studies (N = 13,599 participants), in which the majority were patients with genotype 1 (N = 11,730). Results from these studies suggest that SVR12 is a reliable surrogate for SVR24. The authors suggest that SVR12 may become a new definition for sustained virologic response.

Three disease-specific instruments were used in the included clinical trials to measure HRQoL in hepatitis C patients. The CLDQ-HCV has shown good convergent and construct validities. Limited information was found on the validity of the WPAI questionnaire. No information was found on the validity of FACIT-F in hepatitis C patients. No information could be identified on the MCID of these instruments in hepatitis C.

SF-36, a generic health assessment questionnaire, has shown good construct validity in hepatitis C patients. A mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale has been reported. MCIDs for other dimensions or for the two component scores of the SF-36 were not found in the literature.

APPENDIX 6: SUMMARY OF OTHER STUDIES

1. Objective

Given that the pivotal trial supporting the Health Canada–approved dose for sofosbuvir in genotype 1 chronic hepatitis C (CHC) is limited to a single-arm trial, CADTH appraised randomized controlled trial evidence relevant to this patient population that employed sofosbuvir 400 mg daily for 12 weeks in combination with pegylated interferon plus ribavirin (Peg-INF/RBV).

2. Findings

One randomized double-blind placebo-controlled trial, the PROTON study, was identified.[37,53,54]

Study Design

PROTON was a phase 2 trial assessing the benefits and harms of sofosbuvir in combination with pegylated interferon and ribavirin in treatment-naive patients with hepatitis C virus (HCV) genotype 1 (randomized cohort) and HCV genotype 2 or genotype 3 (single-arm cohort). The study was sponsored by the manufacturer and conducted in the United States (22 sites). PROTON did not meet the criteria for inclusion in the systematic review, given that sofosbuvir was used in a response-guided therapy regimen inconsistent with the Health Canada–approved regimen for patients with genotype 1 CHC, as described below.

a) Randomized Cohort

A total of 122 treatment-naive patients with HCV genotype 1, stratified for IL28B status and baseline HCV RNA levels (< 800,000 IU/mL or ≥ 800,000 IU/mL) were randomized to receive sofosbuvir 200 mg once daily (n = 48), sofosbuvir 400 mg once daily (n = 48), or matching placebo (n = 26) together with Peg-INF/RBV for 12 weeks in a 2:2:1 ratio. Sofosbuvir-treated genotype 1 patients who achieved an extended rapid virologic response (eRVR, defined as HCV RNA < lower limit of detection at weeks 4 to 12) received an additional 12 weeks of Peg-INF/RBV, whereas sofosbuvir-treated genotype 1 patients who did not achieve an eRVR received an additional 36 weeks of Peg-INF/RBV. Placebo-treated genotype 1 patients received an additional 36 weeks of Peg-INF/RBV.

b) Single-arm Cohort

25 treatment-naive HCV genotype 2 or genotype 3 patients received open-label sofosbuvir 400 mg once daily with Peg-INF/RBV for 12 weeks.

The primary end point was the safety and/or tolerability of the treatment regimens. Secondary end points included sustained virologic response (SVR) for 12 and 24 weeks (SVR12 and SVR24; defined as HCV RNA < 15 IU/mL 12 and 24 weeks post-treatment.

Sample size was based on the assumption of a 15% eRVR rate in the Peg-INF/RBV group, and at least a 55% eRVR rate in the sofosbuvir+ Peg-INF/RBV group. A sample size of 75 patients (50 patients in either of the experimental groups and 25 patients in the control group) was required to achieve 95% power to establish superiority using a 5% two-sided significance level.

Data for the randomized cohort are presented in this supplemental issue. Comparisons are limited to the sofosbuvir 400 mg treatment regimen versus the placebo regimen. Patient disposition for these two treatment groups is presented in Table 20. One patient randomized to the sofosbuvir 400 mg treatment regimen was not treated because of inadequate venous access to collect blood samples.

TABLE 20: PATIENT DISPOSITION

n (%)	PROTON	
	Sofosbuvir 400 mg + Peg-INF/RBV	Placebo + Peg-INF/RBV
Enrolled	48	26
Enrolled and treated	47	26
Full analysis set	47	26
Completed treatment	42 (89)	15 (58)
Discontinued treatment	5 (11)	11 (42)
Adverse event	3 (6)	2 (8)
Withdrew consent	0	2 (8)
Lost to follow-up	1 (2)	1 (4)
Other[a]	1 (2)	6 (23)
Completed study	45 (96)	15 (58)
Discontinued study	2 (4)	11 (42)
Adverse event	1 (2)	2 (8)
Lost to follow-up	1 (2)	1 (4)
Withdrew consent	0	2 (8)
Other[a]	0	5 (19)
Termination by sponsor	0	1 (4)

Peg-INF/RBV = pegylated interferon plus ribavirin.
[a]Other reasons include lack of efficacy and withdrawal from treatment.

Two patients in the sofosbuvir+Peg-INF/RBV group who had their treatment discontinued due to adverse events (one patient with depression and suicidal ideation, and one patient with an acute myocardial infarction) chose to complete the study. Again in the sofosbuvir+Peg-INF/RBV group, one patient reported to be in the "other" category (includes include lack of efficacy and withdrawal from treatment) was said to have withdrawn from treatment, yet he or she is marked as having completed the treatment and the study (last dose day reported is 99 days).

Population

Patients were included in the randomized cohort if they were between 18 and 70 years of age, had chronic genotype 1 HCV infection documented by at least one measurement of serum HCV RNA ≥ 50,000 IU/mL, and were naive to all hepatitis C antiviral treatment. Patients who were positive for HIV or hepatitis B and those with METAVIR scores F3 or F4[34] were excluded from entering the trial.

Patient characteristics are presented in Table 21. Whereas the majority of patients in the placebo group were male (73%), less than half the patients in the sofosbuvir group were men (45%). On average, the patients in the placebo group were younger by approximately three years. Most patients had the 1a genotype subtype (75% and 77% for the sofosbuvir and placebo groups, respectively).

TABLE 21: PATIENT CHARACTERISTICS

	PROTON	
	Sofosbuvir 400 mg + Peg-INF/RBV N = 47	Placebo + Peg-INF/RBV N = 26
Age, mean years (SD)	51.4 (9.4)	48.6 (9.4)
Male, n (%)	21 (45)	19 (73)
Baseline HCV RNA $\log_{10}$ (IU/mL), mean (SD)	6.4 (0.8)	6.5 (0.8)
Genotype, n (%)		
1a	35 (75)	20 (77)
1b	12 (26)	6 (23)
IL28B, n (%)		
CC	18 (38)	11 (42)
CT	19 (40)	11 (42)
TT	10 (21)	4 (15)

HCV = hepatitis C virus; Peg-INF/RBV = pegylated interferon plus ribavirin; RNA = ribonucleic acid; SD = standard deviation.

Efficacy

The majority of patients receiving sofosbuvir 400 mg (92%) achieved an eRVR and received an additional 12 weeks of Peg-INF/RBV treatment. This meant that 8% of sofosbuvir-treated genotype 1 patients who did not achieve an eRVR received an additional 36 weeks of Peg-INF/RBV.

SVR12 and SVR24 rates were higher in the sofosbuvir group (92%) compared with the placebo group (58%). Three patients (6%) in the sofosbuvir group experienced an off-treatment relapse, compared with none in the placebo group (Table 22). Two of these patients had not completed treatment due to adverse events.

Sofosbuvir-treated patients with HCV genotype 1a and with IL28B CC had higher SVR12 rates compared with those with genotype 1b and IL28B non-CC, respectively (Table 23). Nonetheless, even these harder-to-treat patients achieved high SVR rates. However, subgroup analyses results should be interpreted with caution, as the sample size in the subgroups was small.

TABLE 22: EFFICACY RESULTS

	PROTON	
	Sofosbuvir 400 mg + Peg-INF/RBV N = 47	Placebo + Peg-INF/RBV N = 26
eRVR, n (%)	43 (92)	5 (19)
SVR12, n (%)	43 (92)	15 (58)
95% CI, %	77, 98	37, 77
SVR24, n (%)	43 (92)	15 (58)
95% CI, %	77, 98	37, 77
Off-treatment relapses, n (%)	3 (6)	0

CI = confidence interval; eRVR = extended rapid virologic response; Peg-INF/RBV = pegylated interferon plus ribavirin; SVR12 = sustained virologic response, 12 weeks; SVR24 = sustained virologic response, 24 weeks.

TABLE 23: SVR12 BY SUBGROUPS

n/N (%)	PROTON	
	Sofosbuvir 400 mg + Peg-INF/RBV N = 47	Placebo + Peg-INF/RBV N = 26
Genotype		
1a	33/35 (94)	11/20 (55)
1b	10/12 (83)	4/6 (67)
IL28B		
CC	18/18 (100)	8/11 (73)
Non-CC	25/29 (86)	7/15 (47)

Peg-INF/RBV = pegylated interferon plus ribavirin; SVR12 = sustained virologic response, 12 weeks.

Harms

The most common adverse event reported in both treatment groups was fatigue, with more than 60% of patients reporting this adverse event (Table 24). Despite the shorter treatment duration for the majority of patients in the sofosbuvir group, compared with the placebo group, a higher proportion of patients in the sofosbuvir group reported gastrointestinal adverse events (nausea, vomiting, and diarrhea), rash, neutropenia, and pyrexia. Anemia was reported in a higher proportion of patients in the placebo group. Serious adverse events and withdrawals due to adverse events were infrequent. No deaths were reported.

TABLE 24: HARMS

n (%)	PROTON	
	Sofosbuvir 400 mg + Peg-INF/RBV N = 47	Placebo + Peg-INF/RBV N = 26
Adverse Events (≥ 15%)	46 (98)	26 (100)
Fatigue	32 (68)	16 (62)
Nausea	21 (45)	9 (35)
Headache	20 (43)	15 (58)
Chills	19 (40)	10 (39)
Insomnia	15 (32)	9 (35)
Rash	15 (32)	4 (15)
Neutropenia	14 (30)	5 (19)
Pain	12 (26)	8 (31)
Myalgia	11 (23)	6 (23)
Diarrhea	11 (23)	2 (8)
Pyrexia	10 (21)	2 (8)
Anemia	8 (17)	7 (27)
Irritability	7 (15)	5 (19)
Vomiting	7 (15)	2 (8)
Decreased appetite	6 (13)	4 (15)
Cough	6 (13)	3 (12)
Arthralgia	5 (11)	5 (19)
Dyspnea	5 (11)	4 (15)
Dyspnea	5 (11)	4 (15)
Dizziness	5 (11)	3 (12)

n (%)	PROTON	
	Sofosbuvir 400 mg + Peg-INF/RBV N = 47	Placebo + Peg-INF/RBV N = 26
Pruritus	5 (11)	3 (12)
Back pain	2 (4)	5 (19)
Serious Adverse Events	3 (6)	1 (4)
Acute myocardial infarction	1 (2)	0
Lymphangitis	1 (2)	0
ST-segment elevation and chest pain	0	1 (4)
Depression and suicidal ideation	1 (2)	0
Withdrawals due to Adverse Events	3 (6)	3 (12)
Death	0	0

Peg-INF/RBV = pegylated interferon plus ribavirin.

3. Summary

PROTON was a phase 2 trial assessing the benefits and harms of sofosbuvir in treatment-naive genotype 1 CHC patients with low fibrosis scores (F0 to F2). The trial randomized patients with genotype 1 HCV (randomized cohort) to sofosbuvir 200 mg once daily (n = 48), sofosbuvir 400 mg once daily (n = 48), or matching placebo (n = 26) together with Peg-INF/RBV; sofosbuvir-treated patients received additional Peg-INF/RBV treatment (12 or 36 weeks) based on virologic response.

Considering only the sofosbuvir 400 mg and the placebo treatment regimens, SVR12 rates were higher in the sofosbuvir group (92%) compared with the placebo group (58%). Three patients (6%) in the sofosbuvir group experienced an off-treatment relapse; however, two of the patients had discontinued treatment early. Despite the shorter treatment duration for the majority of patients in the sofosbuvir group, compared with the placebo group, a higher proportion of patients in the sofosbuvir group reported gastrointestinal adverse events (nausea, vomiting, and diarrhea), rash, neutropenia, and pyrexia. Few patients withdrew from the trial due to adverse events. No deaths were reported.

APPENDIX 7: SUMMARY OF COMPARATORS

1. Objective

The manufacturer conducted a network meta-analysis (NMA)[37] based on a systematic review to compare the clinical efficacy of sofosbuvir with boceprevir and telaprevir-based triple therapies in treatment-naive chronic hepatitis C (CHC) genotype 1 patients. This brief provides a summary and critical appraisal of the methods and main findings of the NMA.

2. Summary of Network Meta-analysis

Given the lack of RCT evidence directly comparing the available DAAs in combination with Peg-INF/RBV), the manufacturer conducted an NMA to estimate the comparative efficacy of sofosbuvir (SOF) with boceprevir (BOC), and telaprevir (TEL) based on the sustained virologic response (SVR) outcome.

Methods

a) Eligibility Criteria

Inclusion criteria for the systematic review consisted of the following: RCTs in adult treatment-naive genotype-1 CHC patients comparing any of the DAAs (SOF, BOC, or TEL) plus Peg-INF/RBV against each other or against Peg-INF/RBV alone were included in the primary model; in addition, clinical trials that included any of the DAAs or Peg-INF/RBV and that either did not have a control intervention at all or did not have a control intervention of interest were considered in the secondary model. Trials enrolling patients coinfected with HIV, hepatitis B, HCV genotype 2 or 3, non-adult populations, treatment-experienced patients, predominantly severe disease state (e.g., cirrhosis), or trials that did not assess approved treatment regiments of BOC and TEL were excluded.

b) Network Meta-analysis

Two Bayesian NMA models were used to analyze the outcome of interest using a primary model and a secondary model. In the primary model, different durations of the triple therapy regimens were not combined into single treatment nodes but were kept separate; in addition, different regimens of dual Peg-INF/RBV therapy, pegylated interferon alpha-2a plus ribavirin (PaR) and pegylated interferon alpha-2b plus ribavirin (PbR), were considered to have different treatment effects and thus were kept separate; a sustained virologic response for 12 and 24 weeks (SVR12 and SVR24, respectively) were considered to be equivalent.

The secondary model was an extension of the primary model. This model incorporated data from the pegylated interferon trials, which compare pegylated interferon with a control (e.g., non-pegylated interferon). It also incorporated single-arm data from clinical trials of DAAs that did not have a control group. In this model, SVR12 and SVR24 were considered to be different; PaR and PbR were also kept separate. For the single-arm trials using active DAAs (SOF or TEL), the expected odds ratio (OR) was obtained using the SVR associated with the active DAA and the mean control group that was established from all trials including a Peg-INF/RBV group.

All outcomes were analyzed as dichotomous outcomes and effect sizes were reported as ORs. The NMA was fitted using a random effects model. A flat normal prior distribution with a mean of 0 and variance of 1,000 for the log OR of treatment k relative to the baseline treatment was assumed. In addition, a log-normal prior distribution with mean −3.02 and standard deviation of 1.85 was used for the between-study variance.

c) Study and Patient Characteristics

Ten trials were included in the primary model (two trials included SOF, two trials included TEL, two trials included BOC, and four trials compared PaR with PbR). In the secondary model, as well as the 10 trials included in the primary model, 27 additional trials were included (one single-arm trial using SOF, one trial using TEL, and 25 single-arm trials reporting data for SVR12 or SVR24 when PaR or PbR were used). Included studies evaluated the different interventions with different treatment durations.

All studies included in the primary model were randomized controlled studies. Included studies evaluated the different interventions with different treatment durations. Table 25 below presents the treatment duration used in the included studies. Dosing criteria were not completely clear, as the manufacturer's report mentioned only the antiviral dose for the DAAs without specifying total daily dose, while for Peg-INF/RBV, the dose and total daily dose were not specified. Figure 2 and Figure 3 below present network diagrams for the primary model and the secondary model, respectively.

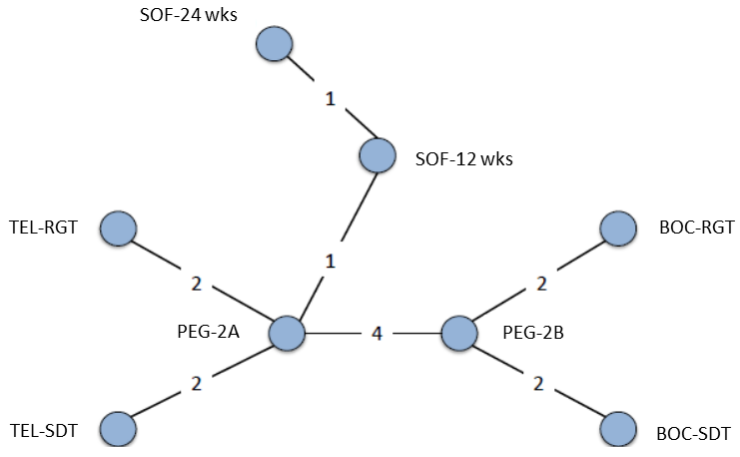
Patient baseline characteristics were not reported.

TABLE 25: DOSING CRITERIA AND TREATMENT DURATION USED FOR INCLUDED STUDIES

DAA Dose	SOF	TEL	BOC
	400 mg	750 mg	800 mg
DAA duration			
	12 weeks, or 24 weeks[a]	12 weeks	24 weeks, or 44 weeks[a]
Peg-INF/RBV duration when used in combination with DAA (total treatment duration)			
	12 weeks, or 24 weeks,[a] or 48 weeks[a]	48 weeks,[a] or RGT (24 or 48 weeks)	48 weeks,[a] or RGT (28 or 48 weeks)
Peg-INF/RBV duration when used alone (total treatment duration)			
48 weeks			

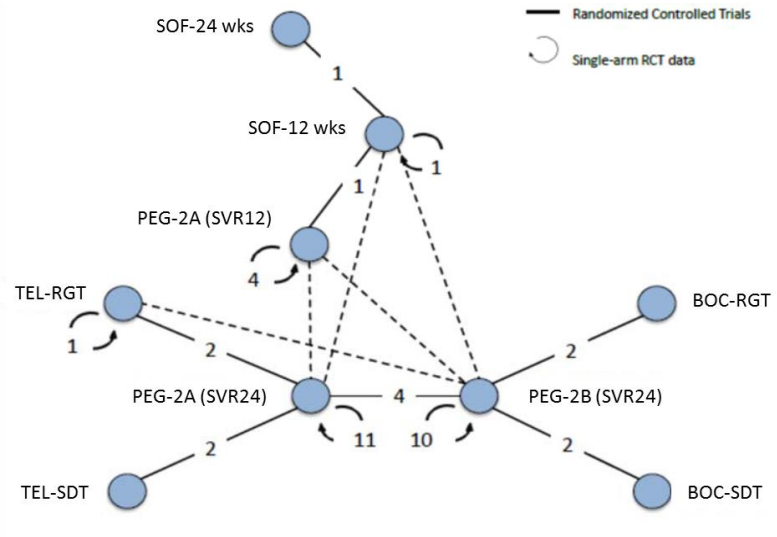
BOC = boceprevir; DAA = direct-acting antiviral; Peg-INF = pegylated interferon; Peg-INF/RBV = pegylated interferon plus ribavirin; RGT = response-guided therapy; RVB = ribavirin; SOF = sofosbuvir; TEL = telaprevir.
[a]Not Health Canada–recommended duration for treatment-naive patients.

FIGURE 2: NETWORK DIAGRAM FOR THE PRIMARY MODEL (ONLY RANDOMIZED CONTROLLED TRIALS INCLUDED)



BOC = boceprevir; PEG-2A = pegylated interferon alpha-2a; PEG-2B = pegylated interferon alpha-2b; RGT = response-guided therapy; SDT = standard-duration therapy; SOF-12 wks = sofosbuvir for 12 weeks; SOF-24 wks = sofosbuvir for 24 weeks; TEL = telaprevir.

FIGURE 3: NETWORK DIAGRAM FOR THE SECONDARY MODEL (INCLUDED RANDOMIZED CONTROLLED TRIALS AND SINGLE-ARM DATA)



BOC = boceprevir; PEG-2A = pegylated interferon alpha-2a; PEG-2B = pegylated interferon alpha-2b; RGT = response-guided therapy; SDT = standard-duration therapy; SOF-12 wks = sofosbuvir for 12 weeks; SOF-24 wks = sofosbuvir for 24 weeks; SVR12 = sustained virologic response at 12 weeks post-therapy; SVR24 = sustained virologic response at 24 weeks post-therapy; TEL = telaprevir.

Results

a) Sustained Virologic Response from the Primary Model

The NMA results for SVR (12 or 24) of SOF, TEL, and BOC triple therapy versus each other or versus PaR dual therapy from the primary model using RCTs only are presented in Table 26 below.

The estimated ORs and the 95% credible interval (CrI) for triple therapy with SOF, TEL, and BOC, except for BOC-RGT, were greater than 1 when compared with PaR dual therapy for 48 weeks, indicating that the triple therapy with all DAAs included in this analysis, except for BOC-RGT, resulted in significantly higher SVRs compared with PaR therapy. However, when the DAA triple therapies were compared against each other, the SVR achieved with SOF was not significantly different from TEL or BOC. No results were provided for the comparison versus PbR.

TABLE 26: RESULTS FROM THE NETWORK META-ANALYSES FOR SUSTAINED VIROLOGIC RESPONSE (12 OR 24) FROM THE PRIMARY MODEL

Comparison	OR (95% CrI)
Versus PaR	
SOF12	8.67 (1.88 to 45.4)
SOF24	9.41 (1.27 to 73.3)
BOC-SDT	2.69 (1.07 to 5.99)
BOC-RGT	2.22 (0.73 to 5.62)
TEL-SDT	3.32 (1.12 to 9.83)
TEL-RGT	3.77 (1.46 to 9.44)

Comparison	OR (95% CrI)
SOF versus TEL or BOC	
SOF12 vs. BOC-SDT	3.29 (0.58 to 21.5)
SOF12 vs. BOC-RGT	3.97 (0.67 to 29.0)
SOF12 vs. TEL-SDT	2.61 (0.40 to 18.7)
SOF12 vs. TEL -RGT	2.28 (0.39 to 15.2)
SOF24 vs. BOC-SDT	3.55 (0.42 to 33.1)
SOF24 vs. BOC-RGT	4.33 (0.48 to 44.3)
SOF24 vs. TEL -SDT	2.83 (0.29 to 28.6)
SOF24 vs. TEL -RGT	2.51 (0.28 to 24.2)

BOC = boceprevir; CrI = credible interval; OR = odds ratio; PaR = pegylated interferon alpha-2a plus ribavirin; RGT = response-guided therapy; SDT = standard-duration therapy; SOF = sofosbuvir; SOF12 = sofosbuvir 12 weeks; SOF24 = sofosbuvir 24 weeks; TEL = telaprevir.

b) Sustained Virologic Response from the Secondary Model

The NMA results from the secondary model, which included single-arm data and adjusted for SVR time point for SOF, TEL, and BOC triple therapy versus each other or versus PaR dual therapy, are presented in Table 27 below. The NMA results of SVR12 and SVR24 from the secondary model for SOF, TEL, and BOC triple therapy versus PaR and PbR are presented in Table 28 below.

The estimated ORs and the 95% CrI for triple therapy with SOF, TEL, and BOC were greater than 1 when compared with PaR dual therapy for 48 weeks, indicating that the triple therapy with all DAAs included in this analysis resulted in significantly higher SVRs compared with PaR therapy.

When the DAA triple therapies were compared against each other, the estimated ORs and the 95% CrI for sofosbuvir used for 12 weeks (SOF12) or sofosbuvir used for 24 weeks (SOF24) were greater than 1 when compared with BOC-SDT, BOC and response-guided therapy (RGT), TEL and standard-duration therapy (SDT), and TEL-RGT, indicating that SOF has significantly higher SVRs compared with BOC and TEL.

Odds ratios from the NMA for SVR 12 for the comparison SOF, TEL, and BOC triple therapy versus PaR and PbR were lower than those for SVR 24. In addition, ORs for the comparison against PbR were higher than those generated from the comparison versus PaR Table 28.

TABLE 27: RESULTS FROM THE NETWORK META-ANALYSES FOR SUSTAINED VIROLOGIC RESPONSE FROM THE SECONDARY MODEL

Comparison	OR (95% CrI)
Versus PaR	
SOF12	8.34 (4.83 to 14.3)
SOF24	9.02 (4.89 to 17.4)
BOC-SDT	2.12 (1.39 to 3.47)
BOC-RGT	1.77 (1.08 to 3.10)
TEL-SDT	2.26 (1.11 to 4.66)
TEL-RGT	3.03 (1.76 to 5.30)

Comparison	OR (95% CrI)
SOF versus TEL or BOC	
SOF12 vs. BOC-SDT	3.96 (2.07 to 7.29)
SOF12 vs. BOC-RGT	4.70 (2.34 to 9.38)
SOF12 vs. TEL-SDT	3.66 (1.62 to 8.60)
SOF12 vs. TEL-RGT	2.77 (1.41 to 5.61)
SOF24 vs. BOC-SDT	4.21 (2.14 to 8.52)
SOF24 vs. BOC-RGT	5.05 (2.44 to 10.6)
SOF24 vs. TEL-SDT	4.05 (1.61 to 9.81)
SOF24 vs. TEL-RGT	2.97 (1.45 to 6.37)

BOC = boceprevir; CrI = credible interval; OR = odds ratio; PaR = pegylated interferon alpha-2a plus ribavirin; RGT = response-guided therapy; SDT = standard-duration therapy; SOF = sofosbuvir; SOF12 = sofosbuvir for 12 weeks; SOF24 = sofosbuvir for 24 weeks; TEL = telaprevir.

TABLE 28: RESULTS FROM THE NETWORK META-ANALYSES FOR SVR12 AND SVR24 FROM THE SECONDARY MODEL FOR SOF, TEL, AND BOC TRIPLE THERAPY VERSUS PAR AND PBR

Comparison	SVR12 OR (95% CrI)	SVR24 OR (95% CrI)
Versus PaR		
SOF12	8.28 (4.76 to 14.9)	10.6 (1.88 to 18.1)
SOF24	8.93 (4.66 to 17.5)	11.4 (1.27 to 21.2)
BOC-SDT	2.12 (1.39 to 3.47)	2.69 (1.90 to 40.5)
BOC-RGT	1.77 (1.08 to 3.10)	2.25 (1.45 to 3.70)
TEL-SDT	2.26 (1.11 to 4.66)	2.87 (1.47 to 5.64)
TEL-RGT	3.03 (1.76 to 5.30)	3.83 (2.42 to 6.07)
Versus PbR		
SOF12	10.9 (6.29 to 20.2)	13.9 (8.41 to 23.6)
SOF24	11.9 (6.38 to 23.1)	15.0 (8.34 to 27.8)
BOC-SDT	2.78 (1.82 to 4.57)	3.51 (2.49 to 5.39)
BOC-RGT	2.32 (1.41 to 4.10)	2.94 (1.90 to 4.84)
TEL-SDT	2.97 (1.46 to 6.13)	3.76 (1.93 to 7.38)
TEL-RGT	3.97 (2.29 to 6.95)	5.02 (3.16 to 8.06)

BOC = boceprevir; CrI = credible interval; OR = odds ratio; PaR = pegylated interferon alpha-2a plus ribavirin; PbR = pegylated interferon alpha-2b plus ribavirin; RGT = response-guided therapy; SDT = standard-duration therapy; SOF = sofosbuvir; SOF12 = sofosbuvir for 12 weeks; SOF24 = sofosbuvir for 24 weeks; SVR12 = sustained virologic response, 12 weeks; SVR24 = sustained virologic response, 24 weeks; TEL = telaprevir.

3. Critical Appraisal of Network Meta-analysis

The quality of the manufacturer-submitted NMA was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[55] Details and commentary for each of the relevant items identified by ISPOR are provided in Table 28.

Strengths

The NMA appears to satisfy some of the ISPOR criteria. It was based on a systematic search to identify all relevant studies. The analysis in the primary model was conducted using an appropriate and well-reported methodology (i.e., Bayesian NMA models created with WinBUGS). The outcome measure assessed in the NMA was clinically relevant.

Limitations

The literature search was undertaken on the July 21, 2013, which made it more than six months old at time of writing, and there may have been studies published since that date. Treatment regimens not recommended by Health Canada were included in the analyses, which may yield different results than if only Health Canada–recommended regimens were used. No sensitivity analysis was performed using only Health Canada–recommended regimens.

In the secondary model, in order to estimate the OR for the single-arm NEUTRINO study, data from 25 single-arm trials were included in the analysis, which might have introduced bias, where the manufacturer assumed that the SVR rate in the Peg-INF/RBV group is the mean of the control group established from all trials that included a Peg-INF/RBV group; however, the manufacturer could have used patient-level data from the NEUTRINO study to match with a patient population having similar characteristics, and then estimate the response in the Peg-INF/RBV group. In addition, the manufacturer is assuming that the treatment groups across all trials are highly homogeneous with regard to the percentage of patients achieving SVR in the Peg-INF/RBV; however, in the 12 single-arm studies of PaR, the SVR rate ranged from 44% to 58%, and in the 10 single-arm studies of PbR, the SVR rate ranged from 27% to 50%, indicating that SVR proportions for the Peg-INF/RBV group from all trials are not homogeneous. In addition, the manufacturer adjusted SVR12 and SVR24 for Peg-INF/RBV groups assuming that SVR12 is lower than SVR24 in this treatment group; however, this adjustment was based on a single study only. For all the reasons listed above, the Common Drug Review (CDR) reviewer did not consider the analysis done by the second model as valid. Finally, the CDR reviewer added the NEUTRINO study to the primary model and assumed that there was a control group with an equal number of participants as the SOF+Peg-INF/RBV treatment group, and assumed that the SVR rate in the Peg-INF/RBV group would be the same as that observed in the Peg-INF/RBV group of the PROTON study (57.7%); using the assumption above, the CDR reviewer found that the SVR achieved with SOF was not significantly different from TEL, and that only SOF-12 is significantly better than BOC, while SOF-24 is not significantly different from BOC.

Treatment durations other than Health Canada recommendation for the DAA or Peg-INF/RBV were used in the model, especially for sofosbuvir; in this case, in the primary model no Health Canada–recommended dose was used due to the lack of suitable RCT. Using doses other than the Health Canada–recommended dose, which includes the extension of duration of DAA or Peg-INF/RBV intake, would impact the results, where a higher SVR could have been estimated.

Patient characteristics and study characteristics in the individual studies were not reported; hence, it is not possible to assess if these characteristics were similar across the included studies. Risk of bias in the included studies was not assessed. Hence, it was not possible to assess whether the results of the NMA were biased by the inclusion of studies having internal validity issues. Also, it was not clear if appropriate dosage was used, where antiviral dose was only reported without mention of the frequency per day.

Heterogeneity is a significant concern for the evaluation of the validity of findings based on this NMA; however, no sensitivity analyses were performed to verify the robustness of the model. The possibility

of differences in treatment effects due to heterogeneity alone cannot be completely excluded; that is, the results presented may be biased due to a lack of control of between trial heterogeneity.

As with all NMAs, a non-significant difference between treatments may not necessarily imply that the treatments are equivalent or non-inferior. In addition, measures of effect were reported as ORs only. ORs may bias the estimate of relative risk (RR) when the event rate is greater than 10%. The higher the event rate, the more misleading it may be to interpret ORs as RRs. The manufacturer performed the analysis using a random effect model with informative variance prior, however not estimation for model fit based on the deviance information criterion to see if the model used would fit better than a fixed effect model or a random effect model with vague priors.

The manufacturer did not analyze other outcomes of interest, such as adverse events.

Finally, there are other relevant comparators that have Health Canada approval for the treatment of chronic hepatitis C genotype 1, such as simeprevir, that were not included in the NMA model.

4. Summary

Without head-to-head trial data for SOF versus other DAAs, the manufacturer conducted a Bayesian NMA based on a systematic review of RCTs and single-arm trials to compare SOF with TEL, and BOC in treatment-naive CHC genotype 1 patients. Overall, the systematic review and NMA reported that triple therapy with any of the three DAAs (SOF, TEL, and BOC) were more effective than Peg-INF/RBV dual therapy in terms of SVR. In the primary model, no significant differences in efficacy between SOF and TEL or between SOF and BOC were reported, while in the secondary model, SOF was significantly better than TEL and BOC; however, there are many limitations in this model and results could be biased. Although the NMA demonstrated sufficient methodological rigour on a number of criteria, there were some important limitations. These included the lack of reporting of patient and study characteristics to determine suitability for conducting NMA, and not assessing for inconsistency, heterogeneity, and model fit, in addition to the concerns regarding the methods used in the secondary model. These issues, in addition to the lack of any head-to-head studies, render uncertain the comparative efficacy of SOF against TEL and BOC.

TABLE 29: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• A clear rationale for the review and a clear research question that pertain to the NMA were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs were clearly stated and seem appropriate. • Several databases were searched, including MEDLINE, Embase, and The Cochrane Central Register of Controlled Trials. • Search strategy was well reported. • Inclusion and exclusion process and data extraction methods used were clearly reported. • Risk of bias in individual studies was not assessed.
3.	Are the outcome measures described?	• Outcome assessed in the NMA was clearly defined.

ISPOR Checklist Item		Details and Comments
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description and justification of the statistical model used was provided, but methods used in the secondary model might not be appropriate and results might be biased. • The manufacturer fitted only a random effects model using informative priors. The DIC that tests the goodness of fit models was not reported, and the model used was not compared with other models, such as fixed effect model, to see which model fit better. • A Bayesian approach was used and informative priors were chosen, so observed data were driven by the prior chosen. No analysis was done using non-informative priors to see how results would differ. • It was not possible to compare direct evidence with the indirect evidence due to the absence of head-to-head trials. In addition, the models were conducted without covariate adjustment for patient or study characteristics, and hence assessment and control of potential bias or inconsistency was insufficient. • ORs were used to present the findings.
5.	Are sensitivity analyses presented?	• No sensitivity analyses were performed. • No sensitivity analysis was undertaken on Health Canada–recommended dose only.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• Identification and selection of full-text studies for the NMA were well reported, as well as presented in a PRISMA flowchart. • A table with study characteristics was provided; however, total daily intake of DAAs was not clear. In addition, dose and daily intake of Peg-INF/RBV was not specified. • No table of patient characteristics was provided. • A figure showing the network of studies was provided. • Raw data by study and treatment as used in the NMA was available.
7.	Does the study describe an assessment of model fit?	• DICs were not reported.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for SVR, including point estimates and 95% CrIs.
9.	Sensitivity/scenario analyses	• No sensitivity analyses results were reported.
10.	Does the discussion include the following? • Description/summary of main findings • Internal validity of analysis External validity • Implications of results for target audience	• A description of main findings was presented in the Conclusion section. • A discussion took place about the validity of the secondary model, but the CDR reviewer disagreed with the reasoning provided, especially about the highly homogeneous SVR rate of the Peg-INF/RBV group; the CDR reviewer found that these data are highly heterogeneous as they vary between 27% and 58%. • A discussion was held on the implication of results for target audience and its impact. Also discussed was the need for an economic decision model to present the real impact of SOF.

CrI = credible interval; CDR = Common Drug Review; DAA = direct-acting antiviral agent; DIC = deviance information criterion; ISPOR = International Society for Pharmacoeconomic and Outcomes Research; NMA = network meta-analysis; OR = odds ratio; Peg-INF/RBV = pegylated interferon plus ribavirin; RCT = randomized controlled trial; SOF = sofosbuvir; SVR = sustained virologic response.

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