Common Drug Review
Clinical Review Report

November 2016

Drug	simeprevir (Galexos) (150 mg)
Indication	chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin 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
Listing request	List with similar criteria to the other currently marketed protease inhibitors (boceprevir and telaprevir) in line with its Health Canada indication
Manufacturer	Janssen Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the CADTH 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient group submissions.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
ARD	adjusted risk difference
AUC	area under the curve
CDEC	CADTH Canadian Drug Expert Committee
CES-D	Center for Epidemiologic Studies Depression Scale
CDR	CADTH Common Drug Review
CHC	chronic hepatitis C
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CrI	credible interval
CUA	cost-utility analysis
DAA	direct-acting antiviral
DB	double-blind
DIC	deviance information criterion
eRVR	extended rapid virologic response
EQ-5D	EuroQol 5-Dimensions Questionnaire
FAS	full analysis set
FSS	Fatigue Severity Scale
HCV	hepatitis C virus
HRQoL	health-related quality of life
ITT	intention-to-treat population
NMA	network meta-analysis
PR	combined peginterferon and ribavirin therapy
RCT	randomized controlled trial
RGT	response-guided therapy
RNA	ribonucleic acid
SAE	serious adverse event
SIM	simeprevir
SVR	sustained virologic response
VAS	Visual Analogue Scale
WDAE	withdrawal due to adverse event
WPAI	Work Productivity and Activity Impairment (questionnaire)

EXECUTIVE SUMMARY

Introduction

Hepatitis C virus (HCV) infection is caused by an enveloped, single-stranded, linear ribonucleic acid (RNA) virus of the *Flaviviridae* family. Before 2011, pegylated interferon plus ribavirin (PR) was the gold standard of therapy to inhibit viral replication in patients with chronic hepatitis C (CHC). Approximately one-half of patients with genotype 1 CHC, the most prevalent type of CHC in Canada, could expect to achieve a sustained viral response (SVR) with PR therapy.

Simeprevir is a direct-acting antiviral (DAA) agent against HCV; it inhibits the HCV NS3/4A protease through a non-covalent, induced-fit binding into the active site of the NS3 protease.[1] In Canada, simeprevir is indicated for the treatment of CHC genotype 1 infection, in combination with peginterferon alfa and ribavirin 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. The recommended dosage is a single 150 mg capsule taken orally once daily in combination with both peginterferon alfa and ribavirin (triple therapy) for 12 weeks, followed by peginterferon alfa and ribavirin (dual therapy) for a further 12 to 36 weeks (the duration is dependent upon the patient's characteristics and response to treatment; i.e., response-guided treatment).

Results and Interpretation

Included Studies

A total of five double-blind (DB) randomized controlled trials (RCTs) comparing simeprevir with placebo (both in combination with PR) in adults with genotype 1 HCV were included in the systematic review. No head-to-head RCTs comparing simeprevir with other DAAs were identified by the CADTH Common Drug Review (CDR). Three of the five studies (QUEST-1 [n = 395], QUEST-2 [n = 393], and PILLAR [n = 386]) were conducted with patients who were treatment-naive, and two of the five studies were conducted with patients who were treatment-experienced (ASPIRE [n = 463] and PROMISE [n = 393]). In ASPIRE, treatment-experienced patients consisted of null responders, partial responders, and relapsers following at least one course of PR therapy, while all of the patients in PROMISE had relapsed following at least one course of PR therapy. In all studies, treatment durations were either 24 or 48 weeks, with a planned followed-up to week 72.

Efficacy

SVR was the primary end point in all trials; however, the time period at which it was measured differed across trials. In QUEST-1, QUEST-2, and PROMISE, the primary end point was SVR12; in ASPIRE, the primary end point was SVR24, while in PILLAR it was SVR at 72 weeks post-baseline.

- In QUEST-1, the proportion of patients achieving SVR12 was 79.5% in the simeprevir group versus 50.0% in the placebo group (adjusted risk difference [ARD], 29.3%; 95% confidence interval [CI], 20.1 to 38.6).
- In QUEST-2, the proportion of patients achieving SVR12 was 81.3% in the simeprevir group versus 50.0% in the placebo group (ARD, 32.2%; 95% CI, 23.3 to 41.2).
- In PILLAR, the proportion of patients achieving SVR at 72 weeks was 77.9% in the simeprevir group versus 64.9% in the placebo group (ARD, 15.4%; 95% CI, –1.1 to 32.0). While the primary end point was not reached, the proportion of patients achieving SVR24 in PILLAR was statistically significantly higher for simeprevir compared with placebo.
- In ASPIRE, the proportion of patients achieving SVR24 was 66.7% in the simeprevir group versus 22.7% in the placebo group (ARD, 49.4%; 95% CI, 30.7 to 68.1).

- In PROMISE, the proportion of patients achieving SVR12 was 79.2% in the simeprevir group versus 36.1% in the placebo group (ARD, 43.8%; 95% CI, 34.6 to 53.0).

Extended rapid virologic response (eRVR) was defined as undetectable plasma HCV RNA levels at weeks 4 and 12 of treatment. Viral relapse was defined as confirmed detectable plasma HCV RNA during follow-up in patients who had had undetectable plasma HCV RNA (< 25 IU/mL) at the end of treatment. In all trials, greater proportions of patients treated with simeprevir achieved eRVR and lower proportions experienced viral relapse compared with placebo-treated patients; however, no statistical analyses were conducted for these outcomes.

Overall, the EuroQol 5-Dimension scale (EQ-5D) results suggest that the addition of simeprevir does not add to the health-related quality of life (HRQoL) burden, given that the between-treatment differences on the 100-point visual analogue scale (VAS) had a magnitude of only 2 to 3 points at week 12. In both the VAS and valuation index scores, more noticeable between-treatment differences (suggesting more favourable HRQoL in the simeprevir group) were not apparent until week 36. These results should be interpreted with caution for the following reasons: patients' knowledge of their treatment status (based on continuation of treatment beyond 24 weeks) may have influenced their responses, the clinical importance of the between-treatment differences is unclear, and no statistical analyses were performed in the individual studies reporting these data. Mortality was rare and, according to the manufacturer, was not related to the study drug.

Planned subgroup analyses were conducted in QUEST-1, QUEST-2, and PROMISE based on fibrosis stage, response to previous PR therapy (relapse, partial response, null response), and presence or absence of the HCV Q80K mutation. The proportion of patients achieving SVR12 was greater among patients receiving simeprevir compared with those receiving placebo, regardless of the METAVIR fibrosis score and prior response to PR therapy. The proportion of simeprevir-treated patients achieving SVR12 was higher for patients with HCV genotype 1a virus without Q80K mutation compared with those patients with HCV genotype 1a virus with Q80k mutation.

Harms

The majority of patients (> 90%) in all treatment groups reported at least one adverse event (AE) during the initial 12 weeks of treatment; frequencies reported for the entire treatment period were ≥ 94%. The proportion of patients who reported at least one AE during the entire treatment phase was comparable between the placebo and simeprevir treatment groups. In all studies, the most commonly reported AEs were fatigue, headache, and infections and infestations. Based on data reported for the entire treatment period, the proportion of patients experiencing a serious adverse event (SAE) was < 13% across all treatment groups; in the studies of treatment-naive patients, the proportion of patients who experienced at least one SAE was greater in the placebo groups compared with the simeprevir groups, while in the studies of treatment-experienced patients, the proportion of patients who experienced at least one SAE was greater in the simeprevir groups compared with the placebo groups. The percentage of patients who withdrew from the study due to adverse events (WDAEs) was < 2% across all studies and treatment groups. Harms identified in the patient input summary included fatigue, insomnia, nausea, and headaches, all of which were generally similar between-treatment groups (with the exception of a greater proportion of patients in the simeprevir group experiencing nausea in most studies during the entire treatment phase). Compared with PR therapy alone, patients treated with simeprevir plus PR had an increased incidence of neutropenia, pruritus, nausea, and photosensitivity during the first 12 weeks of treatment.

Pharmacoeconomic Summary

Background

Simeprevir is being reviewed for the treatment of CHC genotype 1 infection, in combination with PR 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. The manufacturer submitted a price of $434.55 per day ($36,503 per 12-week regimen).

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis (CUA) comparing simeprevir plus PR with telaprevir plus PR, boceprevir plus PR, and PR alone for patients with CHC infection with genotype 1 according to their treatment history: treatment-naive or treatment-experienced. The analysis was based on two phases: a treatment phase (weeks 0 to 72) and a natural disease progression phase (weeks 72 to lifetime).

Efficacy data, in terms of SVR, were derived from a manufacturer-funded, unpublished, network meta-analysis (NMA). Treatment-naive and treatment-experienced populations were assessed in separate networks. The cumulative incidence of complications (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death) over a patient's lifetime was forecasted using published rates of progression among individuals with CHC. The manufacturer assumed that patients achieving SVR were essentially cured and did not progress to develop complications. The comparative risk of AEs (anemia, neutropenia, rash, pruritus) was obtained from the NMA. Treatment-related utility decrements (based on change in EQ-5D scores observed during treatment with simeprevir) and comparators were applied to reflect the decrease in patients' quality of life while on antiviral therapy (48 weeks). During the natural disease progression phase, utility changes were dependent on whether the patient has achieved SVR or whether the disease is progressing. Health state utility values were derived from Chong et al.[2] The costs of the drugs were obtained from the BC Pharmacare Formulary. The duration of therapy was weighted by the proportion of patients who qualified to receive a shorter duration of therapy in clinical trials using a response-guided therapy (RGT) regimen. The resource utilization pattern related to the monitoring of patients was based on Canadian guidelines, and was cost was determined using standard Ontario sources. The costs required to manage AEs occurring during therapy, as well as HCV and its associated complications, were derived from published sources.

Results of Manufacturer's Analysis

In treatment-naive patients, the manufacturer reported that simeprevir-PR dominated telaprevir-PR (lower total costs and greater clinical benefits), and that simeprevir-PR resulted in an incremental cost-utility ratio (ICUR) of $5,202 per quality-adjusted life-year (QALY) and $32,497 per QALY compared with boceprevir-PR and PR alone, respectively.

In treatment-experienced patients, simeprevir-PR was less expensive but provided fewer QALYs compared with telaprevir-PR; simeprevir-PR dominated boceprevir-PR, and simeprevir-PR resulted in an ICUR of $20,430 per QALY compared with PR alone.

Interpretations and Key Limitations

CDR identified a number of issues with the manufacturer's analyses that could have affected the estimates of cost-effectiveness.

- The cost-effectiveness of simeprevir-PR is largely dependent on the validity of the manufacturer-funded NMAs. Detailed information was lacking on the methods and analyses used in the NMAs; this complicates proper critical appraisal of the NMA and brings uncertainty to the ICURs, especially

in treatment-experienced patients. The manufacturer acknowledged the paucity of data and high uncertainty regarding the estimates in treatment-experienced subpopulations.

- The cost of therapies is affected by the proportion of patients eligible to receive a shorter duration of therapy based on RGT criteria. The base-case analysis submitted by the manufacturer assumed that prior relapsers on telaprevir-PR, as well as prior relapsers and partial responders on boceprevir-PR, would not be eligible to receive shorter therapy, which differs from the Canadian product monograph and clinical practice with these products. Therefore, the base case likely overestimated the total cost of treatment with telaprevir-PR and boceprevir-PR.
- For treatment-experienced patients, the model assumed that SVR rates would not differ across fibrosis stages, which is inconsistent with the results of clinical trials.
- Without boceprevir-PR trial data for the null responder population, the comparative cost-effectiveness of simeprevir-PR and boceprevir-PR in that population is unknown.
- Considering that the prevalence of Q80K polymorphism in Canada might be slightly higher than that observed in clinical trials, if testing for Q80K is not routinely done prior to initiating simeprevir-PR, the ICUR of simeprevir-PR versus its comparators would be increased.

Issues for Consideration

- Costs and resources required for testing for Q80K polymorphism were not included in the analysis. The manufacturer indicated that it will pay for all costs associated with logistics, testing, and reporting of Q80K polymorphism.

Results of CADTH Common Drug Review Analysis

In treatment-naive patients, the parameter with the greatest impact on the results was the comparative SVR rate of simeprevir-PR versus PR obtained from the NMA. When the lower bound of the 95% credible interval (CrI), slightly lower cost for drugs, and RGT criteria based on Canadian label were used, simeprevir-PR was dominated by telaprevir-PR, and simeprevir-PR had an ICUR of $1,077,988 per QALY compared with boceprevir-PR and an ICUR of $45,319 per QALY compared with PR.

In treatment-experienced patients, comparative SVR rates obtained from the NMA also had the greatest impact on the results. In a scenario where slightly lower costs for drugs were used, RGT criteria were based on Canadian label, and the lower 95% CrI of the SVR NMA results for simeprevir-PR versus PR and the upper 95% CrI for boceprevir-PR versus PR and telaprevir-PR versus PR were applied, simeprevir-PR was dominated by telaprevir-PR and boceprevir-PR and resulted in an ICUR of $47,279 per QALY versus PR alone.

In both treatment-naive and treatment-experienced patients, the ICUR of simeprevir-PR versus PR alone was less than $50,000 per QALY in most scenarios performed by CDR. The ICUR of simeprevir-PR compared with other DAA-PR regimens varied widely in sensitivity analyses performed by CDR, which reflects uncertainty surrounding the SVR estimates obtained from the NMA, especially in the treatment-experienced population. Based on CDR reanalysis in which Canadian label dosing and lower drug costs were applied, simeprevir-PR dominated telaprevir-PR and led to an ICUR of $32,147 per QALY versus boceprevir-PR and $35,489 per QALY versus PR alone in treatment-naive patients. In treatment-experienced patients, simeprevir-PR was dominated by telaprevir-PR (greater total costs and fewer clinical benefits). Simeprevir-PR dominated boceprevir-PR and led to an ICUR of $21,240 per QALY versus PR alone.

Conclusions

In five DB RCTs, the proportion of treatment-naive (three trials) and treatment-experienced patients (two trials) who achieved SVR was statistically significantly higher among those treated with simeprevir plus PR compared with PR alone. In four of five trials, the simeprevir treatment regimen was based on RGT, and ≥ 79% of patients qualified for the shortened (24-week) duration of treatment. No statistical analyses of between-treatment differences were conducted for other reported efficacy outcomes, including relapse or HRQoL. The trials were of too short a duration to examine between-treatment differences in hepatic morbidity or mortality. Subgroup analyses revealed that simeprevir-treated patients who had the genotype 1a Q80K mutation were less likely to achieve SVR compared with those who lacked the mutation. The Health Canada–approved monograph for simeprevir indicates that testing for Q80K polymorphism in patients with HCV genotype 1a could be considered when accessible.

Based on the results of the five RCTs, compared with PR therapy alone, patients treated with simeprevir plus PR had an increased incidence of neutropenia, pruritus, nausea, and photosensitivity during the first 12 weeks of treatment. No active comparator RCTs of employing Health Canada–approved regimens of simeprevir were identified; thus, the comparative efficacy and safety of simeprevir versus other DAAs approved for the treatment of genotype 1 CHC is uncertain.

TABLE 1: SUMMARY OF RESULTS FOR STUDIES OF TREATMENT-NAIVE PATIENTS

Outcome	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
SVR 12 weeks						
n/N (%)	[redacted]	210/264 (79.5)	67/134 (50.0)	209/257 (81.3)	51/77 (66.2)	62/77 (80.5)
ARD (95% CI)	[redacted]		32.2[a] (23.3 to 41.2)		NA	
SVR 24 weeks						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	50/77 (64.9)	62/77 (80.5)
ARD (95% CI)	[redacted]		33.2[a] (21.4 to 45.0)		[redacted]	
SVR at 72 weeks						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	50/77 (64.9)	60/77 (77.9)
ARD (95% CI)	[redacted]		[redacted]		[redacted]	
eRVR						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	4/77 (5.2)	58/77 (75.3)
Relapse						
n/N (%)	[redacted]	[redacted]	21/88 (23.9)	[redacted]	11/62 (17.7)	6/69 (8.7)
EQ-5D VAS						
Mean (SE) at baseline, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 12, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
baseline at week 24, N	[redacted]					
Mean (SE) change from baseline at week 48, N	[redacted]					
Mean (SE) change from baseline at week 72, N	[redacted]					
EQ-5D Valuation Index						
Mean (SE) at baseline, (N)	[redacted]					
Mean (SE) change from baseline at week 12, N	[redacted]					
Mean (SE) change from baseline at week 24, N	[redacted]					
Mean (SE) change from baseline at week 48, N	[redacted]					
Mean (SE) change from baseline at week 72, N	[redacted]					
Mortality						
n (%)	0	0	0	2(0.8)	0	0
DISCONTINUED FROM STUDY						
n/N (%)	10/130 (7.7)	21/264 (8.0)	17/134 (12.7)	12/257 (4.7)	6/77 (7.8)	7/77(9.1)
SAEs						
n (%)	[redacted]				10 (13.0)	4 (5.2)
WDAEs						
n (%)	[redacted]				1 (1.3)	1 (1.3)

ARD = adjusted risk difference; CI = confidence interval; EQ-5D VAS = EuroQol 5-Dimensions visual analogue scale; eRVR = extended virologic response; PL = placebo; PR = peginterferon and ribavirin combined therapy; SAE= serious adverse event; SE = standard error; SIM = simeprevir; SVR = sustained virologic response; WDAE = withdrawal due to adverse event.
[a] Statistically significant ($P < 0.05$).

TABLE 2: SUMMARY OF RESULTS FOR STUDIES OF TREATMENT-EXPERIENCED PATIENTS

Outcome	ASPIRE		PROMISE	
	PLPR48 (N = 66)	SIM12PR48 (N = 66)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
SVR 12 weeks				
n/N (%)	[redacted]	[redacted]	48/133 (36.1)	206/260 (79.2)
ARD (95% CI)	[redacted]		43.0 [a] (33.8 to 52.3)	
SVR 24 weeks				
n/N (%)	15/66 (22.7)	44/66 (66.7)	20/64 (31.3)	199/254 (78.3)
ARD (95% CI)	[redacted]		47.1 [a] (34.8 to 59.5)	
SVR at week 72				
n/N (%)	NA		[redacted]	[redacted]
ARD (95% CI)			[redacted]	
eRVR				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Relapse				
n/N (%)	12/27 (44.4)	6/51 (11.8)	45/93 (48.4)	46/249 (18.5)
EQ-5d VAS				
Mean (SE) at baseline, N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 12, N	NR		[redacted]	[redacted]
Mean (SE) change from baseline at week 24, N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 48, N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 72, N	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D Valuation Index				
Baseline, N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) at baseline, N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 12, N	[redacted]		[redacted]	[redacted]
Mean (SE) change from baseline at week 24, N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 48, N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 72, N	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	ASPIRE		PROMISE	
	PLPR48 (N = 66)	SIM12PR48 (N = 66)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
Mortality				
n (%)	0	1 (1.5)	1 (0.8)	1 (0.4)
Discontinued from study				
n/N (%)	7/66 (10.6)	5/66 (7.6)	14/133 (10.5)	10/260 (3.8)
SAEs				
n (%)	[redacted]	[redacted]	10 (7.5)	14 (5.4)
WDAEs				
n (%)	0	1 (1.5)	0	1 (0.4)

ARD = adjusted risk difference; EQ-5D VAS = EuroQol 5-Dimensions visual analogue scale; eRVR = extended virologic response; PL = placebo; PR = peginterferon and ribavirin combined therapy; RD = risk difference; SAE = serious adverse event; SE = standard error; SIM = simeprevir; SVR = sustained virologic response; WDAE = withdrawal due to adverse event.
[a] Statistically significant ($P < 0.05$).

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hepatitis C infection (HCV) is caused by an enveloped, single-stranded, linear ribonucleic acid (RNA) virus of the *Flaviviridae* family. It is estimated that 0.8% or 242,000 Canadians have chronic hepatitis C virus (CHC) infection; however, the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[3] In 2009, 11,357 cases of HCV were reported, mostly due to injection drug use.[4] 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%).[5-7]

Of those infected, approximately 25% (range 15% to 45%) clear their infection spontaneously, and the remainder develop chronic infection.[8-10] Of those with chronic infection, 15% to 25% will develop progressive liver disease, end-stage liver disease, or hepatocellular carcinoma, or will require a liver transplant.[11,12] Male gender, ethanol use, human immunodeficiency virus (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 continue to decline,[13,14] it is expected that liver-related morbidity and mortality will continue to increase over the coming decades as those already infected grow older.[3,15]

1.2 Standards of Therapy

Prior to 2011, pegylated interferon plus ribavirin (PR) was the gold standard of therapy to inhibit viral replication in patients with CHC. Approximately half of patients with genotype 1 CHC, the most prevalent type of CHC in Canada, could expect to achieve a sustained virologic response (SVR) with PR therapy. For patients with genotype 1 CHC, the standard therapy has been PR therapy administered for 48 weeks.[16] Greater understanding of the HCV viral replication cycle has resulted in the development of direct-acting antiviral (DAA) agents that target several types of nonstructural proteins used to support viral replication. The market entry of protease inhibitors (boceprevir, telaprevir) changed the landscape of CHC therapy, and current Canadian treatment guidelines recommend either boceprevir or telaprevir in combination with PR for the treatment of CHC genotype 1 infections.[16] Recently, two new DAA agents have been approved by Health Canada (simeprevir and sofosbuvir). All four of the DAAs require administration in conjunction with PR, but are expected to result in improved virologic response compared with PR alone and may allow for shorter overall duration of therapy in some patient populations.[16] According to the clinical expert consulted on this review, only a small fraction of patients is able and willing to receive PR therapy due to the adverse events (AEs) associated with this therapy.

1.3 Drug

Simeprevir is a DAA against HCV and inhibits the HCV NS3/4A protease through a non-covalent, induced-fit binding into the active site of the NS3 protease.[1] In Canada, simeprevir is indicated for the treatment of CHC genotype 1 infection in combination with PR 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. The recommended dosage is 150 mg orally once a day for 12 weeks in combination with PR, followed by further PR therapy. The actual duration of triple and dual therapy is determined by treatment stopping rules and response-guided therapy (RGT) recommendations based on treatment history and patient response to treatment (see Table 3 and Table 4). Simeprevir must not be used as monotherapy, and should be initiated and monitored by a physician experienced in the management of CHC.[1]

TABLE 3: HEALTH CANADA–RECOMMENDED DURATION OF TREATMENT USING RESPONSE-GUIDED THERAPY

Patient Group	HCV RNA at Week 4	Triple Therapy (SIM + PR)	Dual Therapy (PR)	Total Treatment Duration
Treatment-Naive and Prior Relapsers[a]	**Undetectable**	**First 12 weeks**	**Additional 12 weeks**	**24 weeks**
	< 25 IU/mL but detectable	**First 12 weeks**	**Additional 36 weeks**	**48 weeks**
Prior Non-Responders (Including Partial Responders[b] and Null Responders[c])	**Undetectable or < 25 IU/mL but detectable**	**First 12 weeks**	**Additional 36 weeks**	**48 weeks**

HCV = hepatitis C virus; IU = international unit; PR = peginterferon alfa and ribavirin; RNA = ribonucleic acid; SIM = simeprevir.
[a] Prior relapser: Undetectable HCV RNA at the end of prior interferon-based therapy and detectable HCV RNA during follow-up.
[b] Partial responder: Prior on-treatment ≥ 2 $\log_{10}$ IU/mL reduction in HCV RNA from baseline at week 12 and detectable HCV RNA at the last measurement on-treatment.
[c] Null responder: Prior on-treatment < 2 $\log_{10}$ IU/mL reduction in HCV RNA from baseline at week 12 and detectable HCV RNA at the last measurement on-treatment.
Source: Health Canada product monograph.[1]

TABLE 4: HEALTH CANADA–RECOMMENDED TREATMENT STOPPING RULES

HCV RNA	Action
Treatment week 4: ≥ 25 IU/mL	Discontinue SIM, peginterferon alfa and ribavirin
Treatment week 12: detectable[a]	Discontinue peginterferon alfa and ribavirin (treatment with SIM is complete at week 12)
Treatment week 24: detectable[a]	Discontinue peginterferon alfa and ribavirin

HCV = hepatitis C; IU = international units; RNA = ribonucleic acid; SIM = simeprevir.Source: Health Canada product monograph[1]
[a] Re-evaluation of HCV RNA is recommended in case of detectable HCV RNA after previous undetectable HCV RNA to confirm HCV RNA levels prior to discontinuing HCV treatment. Detectable corresponds to HCV RNA below the lower limit of quantification but detected, or HCV RNA ≥ the lower limit of quantification of the assay used.

Indication under review
Treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin 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
Listing criteria requested by sponsor
List with similar criteria to the other currently marketed protease inhibitors (boceprevir and telaprevir) in line with its Health Canada indication

TABLE 5: KEY CHARACTERISTICS OF SIMEPREVIR, BOCEPREVIR, TELAPREVIR, AND SOFOSBUVIR

	Simeprevir	Boceprevir	Telaprevir	Sofosbuvir
Mechanism of Action	DAA against 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 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 (alfa)-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 HCV that is mediated by a membrane-associated multiprotein 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 pegIFN alfa and 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 RBV	Treatment of CHC genotype 1 infection, in combination with pegIFN alfa and 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 pegIFN alfa and 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 CHC genotype 1 and genotype 4 infection in combination with pegIFN and RBV and treatment of genotype 2 and genotype 3 CHC infection in combination with RBV
Route of Administration	Oral			

	Simeprevir	Boceprevir	Telaprevir	Sofosbuvir
Health Canada–Recommended Dose	150 mg capsule once daily with PR **Treatment-Naive:** Triple therapy for 12 weeks, dual therapy for additional 12 or 36 weeks based on RGT **Treatment-Experienced:** Triple therapy for 12 weeks, plus dual therapy 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 PR. **Treatment-Naive:** PR (dual) therapy for 4 weeks, triple therapy for 24 weeks, dual therapy for a possible additional 20 weeks based on RGT **Treatment-Experienced:** PR (dual) therapy for 4 weeks, and either triple therapy for 32 weeks or triple therapy for 32 weeks plus dual therapy 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: PR (dual) therapy for 4 weeks and triple therapy for 44 weeks	1, 125 mg (three 375 mg tablets) twice daily in combination with PR **Treatment-Naive:** Triple therapy for 12 weeks, dual therapy for additional 12 or 36 weeks based on RGT **Treatment-Experienced:** Triple therapy for 12 weeks, dual therapy for additional 12 or 36 weeks based on RGT (prior relapsers) or triple therapy for 12 weeks, dual therapy for additional 36 weeks (prior partial and null responders) Cirrhotic patients: Triple therapy for 12 weeks, dual therapy for 36 weeks	400 mg tablet, once daily with PR (genotypes 1 and 4) or RBV alone (genotypes 2 and 3) **Treatment-Naive:** Triple therapy for 12 weeks (genotype 1) **Cirrhotic patients:** As per above; no special dosing
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; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; PegIFN = peginterferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RGT = response-guided therapy; RNA = ribonucleic acid.
[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

The objective of this report is to perform a systematic review of the beneficial and harmful effects of simeprevir 150 mg for the treatment of CHC genotype 1 infection in combination with PR 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.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 6.

TABLE 6: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with CHC genotype 1 infection with compensated liver disease, including cirrhosis **Subpopulation:** • Treatment history based on prior PR (treatment-naive, prior relapse, prior partial response, null response) • Fibrosis stage • HIV coinfection • Q80K genotype mutation
Intervention[a]	SIM 150 mg once daily in combination with PR[b]
Comparators[a]	• Placebo in combination with PR[b] • BOC in combination with PR[b] • TEL in combination with PR[b] • SOF in combination with PR[b]
Outcomes	**Key efficacy outcomes:** • SVR • eRVR • 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:** • AEs, SAEs, WDAEs • Harms of special interest (rash, fatigue, anemia, neutropenia, pruritus, depression, sleep loss, gastrointestinal complications, photosensitivity)
Study Design	Published and unpublished RCTs

AE = adverse events; BOC = boceprevir; CHC = chronic hepatitis C; DB = double-blind; eRVR = extended rapid virologic response; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; PR = pegylated interferon plus ribavirin; RCT = randomized controlled trial; RNA = ribonucleic acid; SAE = serious adverse events; SIM = simeprevir; SOF = sofosbuvir; SVR12 = sustained virologic response at 12 weeks; TEL = telaprevir; WDAE = withdrawal due to adverse events.

[a] At Health Canada–recommended dose.

[b] PegIFN alfa-2a or PegIFN alfa-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 simeprevir and Galexos.

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 December 19, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on May 21, 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.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 7; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of 53 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 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

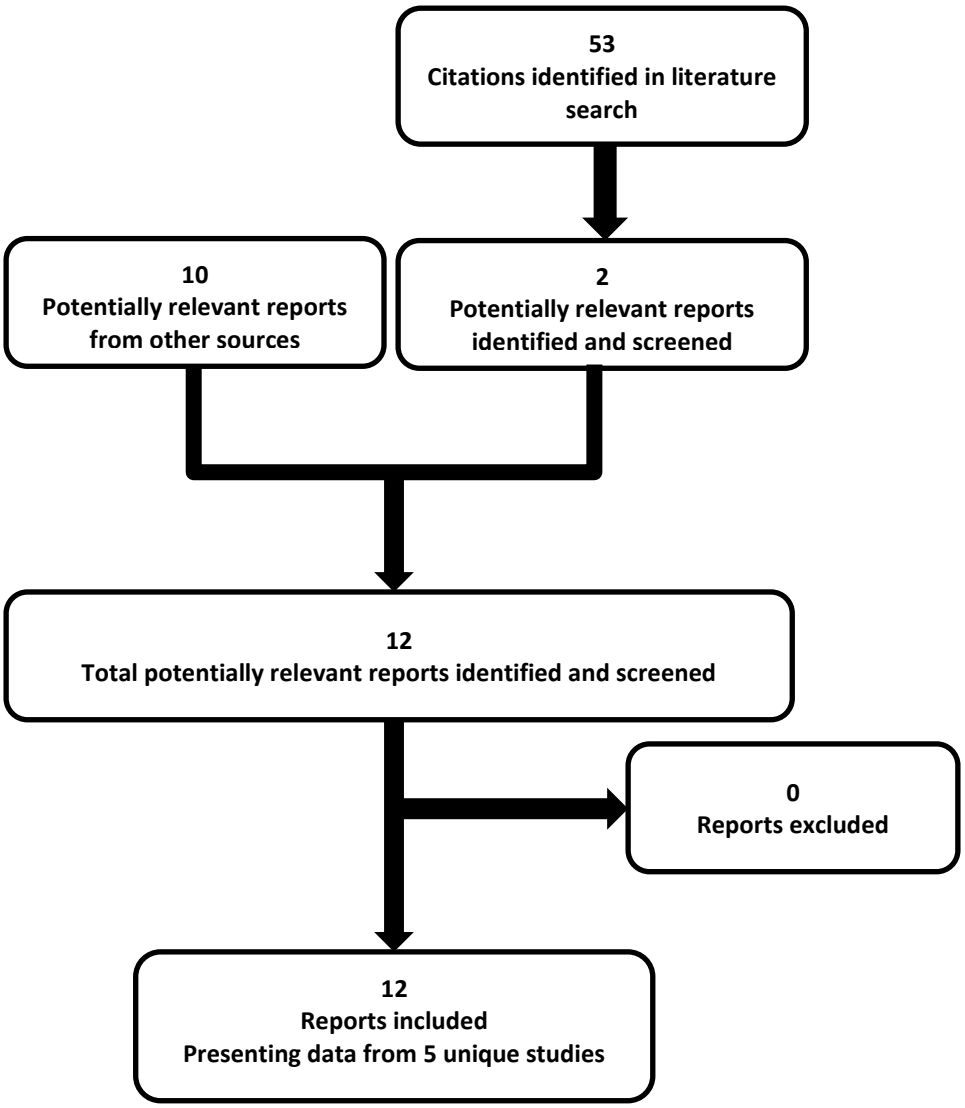

TABLE 7: DETAILS OF INCLUDED STUDIES OF TREATMENT-NAIVE PATIENTS

		QUEST-1	QUEST-2	PILLAR
DESIGNS AND POPULATIONS	**Study Design**	2-arm DB RCT	2-arm DB RCT	5-arm DB RCT
	Locations	Australia, Canada, Germany, Italy, Mexico, New Zealand, Puerto Rico, Romania, Russian Federation, Spain, Ukraine, United Kingdom, and United States	Argentina, Austria, Belgium, Brazil, Bulgaria, France, Germany, Netherlands, Poland, Portugal, Slovakia, Spain, Turkey, and United States	Australia, Austria, Belgium, Canada, Denmark, France, Germany, New Zealand, Norway, Poland, Russia, Spain, and United States
	Randomized (N)	395	393	386
	Inclusion Criteria	• Aged ≥ 18 • Histology consistent with CHC infection (based on liver biopsy within the past 3 years; [redacted] • Confirmed HCV genotype 1 infection • Plasma HCV RNA > 10,000 IU/mL at screening [redacted] • No prior treatment with any approved or investigational drug for the treatment of HCV	• Aged ≥ 18 years • Histology consistent with CHC infection (based on liver biopsy within the past 3 years [redacted] • Confirmed HCV genotype 1 infection • Plasma HCV RNA > 10,000 IU/mL at screening [redacted] • No prior treatment with any approved or investigational drug for the treatment of HCV	• Aged 18 to 70 years • Documented CHC infection as evidenced by all of the following: 1) a liver biopsy demonstrating CHC infection within 2 years of screening; 2) anti-HCV positive; 3) HCV RNA positive • Confirmed HCV genotype 1 infection • Plasma HCV RNA > 100,000 IU/mL at screening • Body weight between 40 and 125 kg • No prior treatment with any approved or investigational drug for the treatment of HCV
	Exclusion Criteria	• Hepatic decompensation • Coinfection with HIV type 1 or type 2 • [redacted]	• Hepatic decompensation • Coinfection with HIV type 1 or type 2 • [redacted]	• Hepatic decompensation or cirrhosis • Coinfection with HIV type 1 or type 2 [redacted]

		QUEST-1	QUEST-2	PILLAR
		[redacted]	[redacted]	[redacted]
DRUGS	**Intervention**	Duration of therapy guided by stopping rules and RGT SIM 150 mg q.d. × 12 wks + PR[a] for 24 or 48 wks	Duration of therapy guided by stopping rules and RGT SIM 150 mg q.d. × 12 wks + PR[a or b] for 24 or 48 wks	Duration of therapy guided by stopping rules and RGT • SIM 75 mg q.d. × 12 wks + PR[a] for 24 or 48 wks • SIM 75 mg q.d. × 24 wks + PR[a] for 24 or 48 wks • SIM 150 mg q.d. × 12 wks + PR[a] for 24 or 48 wks • SIM 150 mg q.d. × 24 wks + PR[a] for 24 or 48 wks
	Comparator(s)	• Placebo for 12 wks + PR[a] for 48 wks	• Placebo for 12 wks + PR[a or b] for 48 wks	• Placebo for 24 wks + PR[a] for 48 wks
DURATION				
	DB treatment	24 or 48 wks treatment		
	Follow-up	Post-therapy follow-up to week 72		
OUTCOMES	**Primary End Point**	SVR12	SVR12	SVR at 72 wks post-baseline
	Other End Points	SVR24 eRVR Relapse HRQoL Fatigue (FSS) Work productivity (WPAI)	SVR24 [redacted] Relapse HRQoL Fatigue (FSS) Work productivity (WPAI)	SVR12 SVR24 eRVR Relapse HRQoL
NOTES	**Publications**	None	None	Fried et al. (2013)[17]

CHC = chronic hepatitis C; DB = double-blind; eRVR = extended rapid virologic response; FSS = Fatigue Severity Scale; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; IU = international units; PR = peginterferon and ribavirin combined therapy; q.d. = once daily; RCT = randomized controlled trial; RGT = response-guided therapy; SIM = simeprevir; SVR = sustained virologic response; wks = weeks; WPAI = Work Productivity and Activity Impairment.Source: Clinical Study Reports.[18-20]
Note: Four additional reports were included.[21-24]
[a] Peginterferon alfa-2a: 180 mcg once weekly and ribavirin: 1,000 or 1,200 mg/day[a] (b.i.d. regimen). For ribavirin, if body weight < 75 kg, total daily dose was 1,000 mg; if body weight ≥ 75 kg, total daily dose was 1,200 mg.
[b] Peginterferon alfa-2b 1.5 mcg/kg (pre-filled pens per weight band) and ribavirin 800 mg/day to 1,400 mg/day[c] (twice dailyregimen). For ribavirin, if body weight ≤ 65 kg, total daily dose was 800 mg; if body weight > 65kg to ≤ 80 kg, total daily dose was 1,000 mg.

TABLE 8: DETAILS OF INCLUDED STUDIES OF TREATMENT-EXPERIENCED PATIENTS

		ASPIRE	PROMISE
DESIGNS & POPULATIONS	**Study Design**	7-arm DB RCT	2-arm DB RCT
	Locations	Australia, Austria, Belgium, Canada, France, Germany, Israel, Poland, Portugal, New Zealand, Norway, Russian Federation, United Kingdom, and United States	Australia, Austria, Belgium, Canada, France, Germany, Italy, New Zealand, Poland, Puerto Rico, Russian Federation, Spain, United Kingdom, and United States
	Randomized (N)	463	394
	Inclusion Criteria	• Aged 18 to 70 years • [redacted] • Confirmed HCV genotype 1 • Plasma HCV RNA > 10,000 IU/mL at screening • [redacted] • At least 1 prior course of PegIFN-a/RBV for at least 12 consecutive weeks and not discontinued therapy due to tolerability.	• Aged ≥ 18 • Confirmed HCV genotype 1 infection • Plasma HCV RNA > 10,000 IU/mL at screening • Liver biopsy performed within 3 years prior to the screening visit with histology consistent with CHC • Patients with bridging fibrosis or cirrhosis had to have an ultrasound taken within 6 months prior to the screening visit with no findings suspicious for hepatocellular carcinoma (HCC) • Received pegIFN-based therapy for at least 24 weeks with documented undetectable HCV RNA at the last measurement on-treatment or an undetectable HCV RNA within 2 months after the actual end of treatment and a subsequent detectable HCV RNA level within 1 year after the last drug intake
	Exclusion Criteria	• Hepatic decompensation • Infection or coinfection with non-genotype 1 HCV, HBV, or HIV [redacted]	• Hepatic decompensation • Coinfection with HIV type 1 or type 2 [redacted] • Hepatitis B

		ASPIRE	PROMISE
DRUGS	**Intervention**	Duration of PR therapy in all arms: 48 weeks • SIM 100 mg q.d. × 12 wks + PR[a] • SIM 100 mg q.d. × 24 wks +PR[a] • SIM 100 mg q.d. × 48 wks + PR[a] • SIM 150 mg q.d. × 12 wks + PR[a] • SIM 150 mg q.d. × 24 wks + PR[a] • SIM 150 mg q.d. × 48 wks + PR[a]	Duration of therapy guided by stopping rules and RGT • SIM 150 mg q.d. × 12 wks, + PR[a] for 24 or 48 wks
	Comparator(s)	• PL × 48 wks + PR[a] for 48 wks	• PL × 12 wks + PR[a] for 48 wks
DURATION	DB treatment	48 wks treatment	24 wks or 48 wks treatment
	Follow-up	Post-therapy follow-up to week 72	
OUTCOMES	**Primary End Point**	SVR24	SVR12
	Other End Points	SVR12 eRVR Relapse [redacted]	SVR24 [redacted] Relapse [redacted] Fatigue (FSS) Work productivity (WPAI)
NOTES	**Publications**	Zeuzem et al. (2014)[25]	Forns et al. (2014) [26]

CHC = chronic hepatitis C; DB = double-blind; eRVR = extended rapid virologic response; FSS = Fatigue Severity Scale; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IU = international unit; pegIFN = peginterferon; PL = placebo; PR = peginterferon and ribavirin combined therapy; q.d. = once daily; RBV = ribavirin; RCT = randomized controlled trial; RGT = response-guided therapy; SIM = simeprevir; SVR = sustained virologic response; wks = weeks; WPAI = Work Productivity and Activity Impairment.

[a] Peginterferon alfa-2a: 180 mcg once weekly and ribavirin: 1,000 mg/day or 1,200 mg/day[a] (b.i.d. regimen). For ribavirin, if body weight < 75 kg: total daily dose was 1,000 mg; if body weight ≥ 75 kg, total daily dose was 1,200 mg.

[b] Peginterferon alfa-2b 1.5 mcg/kg (pre-filled pens per weight band) and ribavirin 800 mg/day to 1,400 mg/day[c] (b.i.d. regimen). For ribavirin, if body weight was ≤ 65 kg, total daily dose was 800 mg; if body weight was > 65kg to ≤ 80 kg, total daily dose was 1,000 mg.

Note: Four additional reports were included.[21-24]

Source: Clinical Study Reports.[27,28]

3.2 Included Studies

3.2.1 Description of Studies

Five multi-centre, randomized, DB placebo-controlled trials met the inclusion criteria for this systematic review, including three phase 3 studies (QUEST-1, QUEST-2, and PROMISE) and two phase II studies (PILLAR and ASPIRE). QUEST-1 (N = 395), QUEST-2 (N = 393), and PILLAR (N = 386) compared simeprevir plus PR with PR alone in treatment-naive patients with CHC due to HCV genotype 1, while ASPIRE (N = 463) and PROMISE (N = 393) compared simeprevir plus PR with PR alone in patients with CHC due to HCV genotype 1 who were treatment-experienced with PR therapy (i.e., patients with prior relapse, partial response, or null response). In all studies, treatment duration was a maximum of 48 weeks with planned follow-up to week 72. However, in three studies (QUEST-1, QUEST-2, and PROMISE), data for the complete patient population are available only up to week 60.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

All five studies exclusively enrolled adults with CHC having confirmed HCV genotype 1; however, two studies (PILLAR and ASPIRE) excluded patients older than 70 years (Table 7 and Table 8). All studies excluded patients coinfected with HIV type 1 or 2, [redacted]. One study (PILLAR) excluded patients with cirrhosis.

Of the two trials that enrolled treatment-experienced patients, one (PROMISE) was restricted to patients with prior relapse. Specifically, the only patients who were included were those who had relapsed after at least 24 weeks of PR therapy with documented undetectable HCV RNA at the last measurement on-treatment, or who had an undetectable HCV RNA level within two months after the actual end of treatment and a subsequent detectable HCV RNA level within one year after the last drug intake.

In contrast, ASPIRE enrolled all eligible patients with at least one prior documented course of PR therapy for at least 12 consecutive weeks that had not been discontinued due to drug intolerance. ASPIRE included prior relapsers, partial responders, and null responders based on the following definitions:

- [redacted]

b) Baseline Characteristics

Across all five studies, the median age ranged from 45 to 52 years, and in all studies the majority of patients were reported as Caucasian (Table 9 and Table 10). There were some notable differences between the studies of treatment-naive and treatment-experienced patients. Studies of treatment-experienced patients included a higher percentage of males, patients with the IL28B genotype, and patients with advanced liver fibrosis based on METAVIR fibrosis scores. (As noted above, one study of treatment-naive patients [PILLAR] excluded patients with cirrhosis [METAVIR fibrosis score = F4]). A notable between-study difference included the higher percentage of patients with Q80K polymorphism in QUEST-1 (23% versus a range of 9% to 13% in the remaining trials).

Baseline characteristics were generally well balanced across treatment groups in all trials, with the exception of some minor imbalance in IL28B genotypes in PILLAR and ASPIRE.

TABLE 9 : SUMMARY OF BASELINE CHARACTERISTICS STUDIES OF TREATMENT-NAIVE PATIENTS

Characteristics	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
Median age in years, (range)	48.0 (20 to 66)	48.0 (19 to 68)	47.0 (18 to 73)	46.0 (18 to 73)	45.0 (21 to 67)	47.0 (18 to 69)
Male, n (%)	74 (56.9)	148 (56.1)	77 (57.5)	140 (54.5)	39 (50.6)	43 (55.8)
Median weight in kg, (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HIV coinfection	NA					
Q80K genotype mutation n/N	30 /129 (23.3)	61/262 (23.3)	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)						
Caucasian	122 (93.8)	227 (86.6)	123 (91.8)	237 (92.2)	74 (96.1)	74 (96.1)
Black	4 (3.1)	27 (10.3)	10 (7.5)	16 (6.2)	3 (3.9)	2 (2.6)
Asian	3 (2.3)	5 (1.9)	1 (0.7)	2 (0.8)	0	0
Other	1 (0.8)	3 (1.2)	0	2 (0.8)	1 (1.3)	0
METAVIR Fibrosis Score						
F0 to F1	50/130 (38.5)	118/260 (45.4)	60/134 (44.8)	130/248 (52.4)	44/77 (57.1)	44/77 (57.1)
F2	40/130 (30.8)	65/260 (25.0)	42/134 (31.3)	65/248 (26.2)	26/77 (33.8)	26/77 (33.8)
F3	23/130 (17.7)	46/260 (17.7)	17/134 (12.7)	36/248 (14.5)	7/77 (9.1)	7/77 (9.1)
F4	17/130 [redacted]	31/260 (11.9)	15/134 [redacted]	17/248 (6.9)	0	0
HCV Genotype 1 Subtype, n/N (%)						
1a	74/130 (56.9)	147/264 (55.7)	54/134(40.3)	105/257 (40.9)	[redacted]	[redacted]
1b	56/130 (43.1)	117/264 (44.3)	77/134 (57.5)	150/257 (58.4)	[redacted]	[redacted]
Other	0	0	[redacted]	[redacted]	[redacted]	[redacted]
IL28B Genotype						
CC	37/130 (28.5)	77/264 (29.2)	42/134 (31.3)	75/257 (29.2)	12/46[a] (26.1)	22/55[a] (40.0)
CT	76/130 (58.5)	150/264 (56.8)	71/134(53.0)	142/257 (55.3)	28/46[a] (60.9)	27/55[a] (49.1)
TT	17/130 (13.1)	37/264 (14.0)	21/134 (15.7)	40/257 (15.6)	6/46[a] (13.0)	6/55[a] (10.9)

CC = homozygous normal genotype; CT = heterozygous genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; NA = not applicable; SIM = simeprevir; PL = placebo; PR = peginterferon and ribavirin combined therapy; TT = homozygous variant genotype.

[a] IL28B data were available only for patients who signed the separate informed consent form.

Source: Clinical Study Reports.[18-20]

TABLE 10: SUMMARY OF BASELINE CHARACTERISTICS STUDIES OF TREATMENT-EXPERIENCED PATIENTS

Characteristics	ASPIRE		PROMISE	
	PLPR48 (N = 66)	SIM12PR48 (N = 66)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
Median age in years, (range)	50.5 (22 to 66)	48.0 (20 to 63)	52.0 (21 to 71)	52.0 (20 to 70)
Male, n (%)	42 (63.6)	45 (68.2)	79 (59.4%)	179 (68.8%)
Median weight in kg, (range)	[redacted]	[redacted]	[redacted]	[redacted]
HIV coinfection		[redacted]		[redacted]
Q80K genotype mutation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior response to PR, n (%)				
Null responder[a]	16 (24.2)	17 (25.8)	NA	
Partial responder[b]	23 (34.8)	23 (34.8)	NA	
Relapser[c]	27 (40.9)	26 (39.4)	133 (100.0)	260 (100.0)
Race, n (%)				
Caucasian	62 (93.9)	61 (92.4)	128 (96.2)	243 (93.5)
Black	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
METAVIR Fibrosis Score, n/N (%)				
F0 to F1	[redacted]	[redacted]	[redacted]	[redacted]
F2	[redacted]	[redacted]	[redacted]	[redacted]
F3	13/64 (20.3)	11/66 (16.7)	15/132 (11.4)	44/250 (17.6)
F4	10/64 (15.6)	13/66 (19.7)	19/132 (14.4)	39/250 (15.6)
HCV Genotype 1 Subtype				
1a	27/66 (40.9)	30/66 (45.5)	54/133 (40.6)	110/260 (42.3)
1b	39/66 (59.1)	36/66 (54.4)	79/133 (59.4)	149/260 (57.3)
Other	0	0	0	1/260 (0.4)
IL28B Genotype				
CC	11/50[d] (22.0)	5/43[d] (11.6)	34/133 (25.6)	62/260 (23.8)
CT	32/50[d] (64.0)	30/43[d] (69.8)	83/133 (62.4)	167/260 (64.2)
TT	7/50[d] (14.0)	8/43[d] (18.6)	16/133 (12.0)	31/260 (11.9)

CC = homozygous normal genotype; CT = heterozygous genotype ; HCV = hepatitis C virus; HIV = human immunodeficiency virus; N/A = not applicable; SIM = simeprevir; PL = placebo; PR = peginterferon and ribavirin combined therapy; TT = homozygous variant genotype.

[a] < 2 log10 IU/mL reduction in HCV RNA compared with baseline at week 12 of the previous PegIFN alfa-2a/b and ribavirin treatment.

[b] ≥ 2 log10 IU/mL reduction in HCV RNA compared with baseline at week 12, but not achieving an undetectable HCV RNA at the end of the previous PegIFN alfa-2a/b and ribavirin treatment.

[c] HCV RNA undetectable at end of the previous treatment with PegIFN alfa-2a/b and ribavirin, but detectable HCV RNA within 24 weeks of follow-up.

[d] IL28B data were available only for patients who signed the separate informed consent form.

Source: Clinical Study Reports.[27,28]

3.2.3 Interventions

In QUEST-1, QUEST-2, and PROMISE, patients were randomized in a 2:1 ratio (stratified by HCV genotype 1 subtype and interleukin-28B [IL28B] genotype) to receive either simeprevir 150 mg or placebo once daily for 12 weeks, all in combination with PR. Total duration of PR therapy was 24 weeks or 48 weeks based on treatment response as per RGT criteria, with patients who achieved HCV RNA less than 25 IU/mL at week 4 and HCV RNA undetectable (< 25 IU/mL) at week 12 receiving the shorter duration of PR therapy.

In PILLAR, patients were randomized in a 1:1:1:1:1 ratio (stratified by HCV genotype 1 subtype, and race) to one of four simeprevir treatment groups or placebo, all in combination with PR. For the purpose of this report, results are presented only for the simeprevir treatment group that employed the Health Canada–recommended dose (150 mg once daily for 12 weeks in combination with PR therapy).[1] Total duration of PR therapy was 24 weeks or 48 weeks based on treatment response, as per RGT criteria, with patients who achieved HCV RNA less than 25 IU/mL at week 4 and HCV RNA undectable (< 25 IU/mL) at weeks 12, 16, and 20 receiving the shorter duration of PR therapy.

In ASPIRE, patients were randomized in a 1:1:1:1:1:1:1 ratio (stratified by HCV genotype 1 subtype and prior PR therapy response [relapse, partial, null]) to one of six simeprevir treatment groups or placebo, all in combination with PR. For the purpose of this report, results are presented only for the simeprevir treatment group that employed the Health Canada–recommended dose (150 mg once daily for 12 weeks in combination with PR therapy).[1] Total duration of PR therapy in all treatment groups was 48 weeks.

In all studies, the doses of PR included peginterferon alfa-2a 180 mcg once weekly and ribavirin 1,000 mg/day (if body weight was less than 75 kg) or 1,200 mg/day (if body weight was greater than 75 kg). In QUEST-2, a second option of PR therapy was also used: peginterferon alfa-2b (1.5 mcg/kg pre-filled pens per weight band) and ribavirin 800 mg/day (if body weight was less than 65kg) or 1,400 mg/day (if body weight was greater than 65 kg) for 12 weeks.

[redacted]

3.2.4 Outcomes

Key outcomes assessed in this systematic review (including SVR, extended rapid virologic response [eRVR], relapse, HRQoL, and mortality) were measured for all patients at days 3 and 7, and at weeks 2, 4, 8, 12, 16, 20, and 24. Patients who stopped PR therapy at week 24 were required to come in for post-therapy follow-up visits at weeks 28, 36, 48, 60 and a final visit at week 72. Patients who continued PR therapy until week 48 were required to return for visits at weeks 28, 36, 48, 60, and 72. Patients who prematurely discontinued all study treatment (simeprevir and PR therapy) prior to week 12 or only PR therapy after week 12 were to return for visits at study drug withdrawal, four weeks after the study drug withdrawal, and every 12 weeks until week 72. In all studies, HCV RNA determination was performed at a central laboratory. Plasma HCV RNA levels were determined using the Roche COBAS TaqMan HCV/HPS v2.0 assay.

a) Sustained Virologic Response

SVR was the primary end point in all trials; however, the time period at which it was measured differed across trials. In QUEST-1, QUEST-2, and PROMISE, the primary end point was SVR12; in ASPIRE, the primary end point was SVR24, and in PILLAR it was SVR at 72 weeks post-baseline. The primary end point in SVR12 was defined as "undetectable plasma HCV RNA at the end of treatment and 12 weeks after the planned end of treatment." Similarly, SVR24 was defined as "undetectable plasma HCV RNA at the end of treatment and 24 weeks after the planned end of treatment." SVR at 72 weeks post-baseline was defined as "patient with undetectable HCV RNA at the end of treatment and at week 72 from baseline." In all studies, "undetectable" was defined as HCV RNA < 25 IU/mL).

b) Extended Rapid Virologic Response

eRVR was defined as "undetectable plasma HCV RNA levels at weeks 4 and 12 of treatment."

c) Relapse

Viral relapse was defined as "confirmed detectable plasma HCV RNA during follow-up in patients who had had undetectable plasma HCV RNA (< 25 IU/mL) at the end of treatment."

d) Health-Related Quality of Life

HRQoL was measured using the EuroQol 5-Dimensions (EQ-5D) scale. The EQ-5D is an HRQoL instrument that measures quality of life on three levels ("no problems," "some problems," and "extreme problems") for five health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For the valuation index, scores are derived from the five dimensions to compute a single index value for health status. The VAS tool ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). Patients completed the EQ-5D instrument at baseline and at weeks 4, 12, 24, 36, 48, 60, and 72. Patients were asked to rate their quality of life at that current moment. Results for both the valuation index and VAS of the EQ-5D are presented in this report.

Work productivity was measured using the Work Productivity and Activity Impairment (WPAI) questionnaire. The WPAI is a six-item validated instrument that consists of four metrics: absenteeism (the percentage of work time missed because of one's health), presenteeism (the percentage of impairment experienced while at work because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health). The WPAI productivity score has a possible range from 0% to 100% and was calculated by multiplying the time spent working with the percentage of productivity impairment when at work; higher WPAI productivity

scores indicate greater impairment in productivity. Patients completed the WPAI questionnaire at baseline and weeks 4, 12, 24, 36, 48, 60, and 72. The recall period for all items was seven days.

e) Mortality

In the safety analysis, mortality was measured as the number of patients who died, regardless of cause. Other efficacy outcomes of interest identified for this systematic review included hepatic-related morbidity outcomes (i.e., histological changes, hepatocellular carcinoma, liver failure, and liver transplant). However, none of these outcomes were assessed in any of the included studies.

f) Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a nine-item scale. The items include 1) "My motivation is lower when I am fatigued;" 2) "Exercise brings on my fatigue;" 3) "I am easily fatigued;" 4) "Fatigue interferes with my physical functioning;" 5) "Fatigue causes frequent problems for me;" 6) "My fatigue prevents sustained physical functioning;" 7) "Fatigue interferes with carrying out certain duties and responsibilities;" 8) "Fatigue is among my most disabling symptoms;" and 9) "Fatigue interferes with my work, family, or social life." The item responses are measured on a 7-point Likert-type scale that ranges from "strongly disagree" to "strongly agree"; higher values indicate the higher influence of fatigue for all items. The nine items are combined into one total score. If the number of missing items is fewer than four, the total score is the mean of the non-missing items. Otherwise the total score is set to missing.

g) Center for Epidemiologic Studies Depression Scale

The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item questionnaire with scores that are based upon the assessment of the dimensions of depressed affect, positive affect, somatic impact, and interpersonal impact of depression. The total score ranges from 0 to 60, with higher scores indicating more and/or more frequent experience of depressive symptoms during the past week

3.2.5 Statistical Analysis

- [redacted]
- In both PILLAR and ASPIRE, no a priori sample size calculations were performed.
- In all studies, the primary analysis for the primary end point was performed using the intention-to-treat (ITT) population. [redacted]
- In all studies, patients with missing data (patients who had undetectable HCV RNA at the end of treatment but who did not have a valid HCV RNA sample at the time of SVR) and patients who did not complete scheduled doses (24 or 48 weeks of randomized treatment) were considered to be treatment failures. Sensitivity analyses for missing information was performed by applying different imputation rules for missing data (imputation by end-of-treatment measurement, imputation by last non-missing post-treatment week, and multiple imputation [QUEST-1, QUEST-2, and PROMISE only]).
- In QUEST-1, QUEST-2, and PROMISE, the primary analysis was performed when all randomized patients had completed the week 60 visit or had discontinued earlier.

- In QUEST-1, QUEST-2, and PROMISE, the Cochran–Mantel–Haenszel (CMH) test controlling for stratification factors genotype subtype and IL28B genotype was used to compare the proportion of patients with SVR12, SVR24 and SVR at week 72 between-treatment groups. In QUEST-2, the CMH test also controlled for type of peginterferon (2a or 2b). A 95% CI was calculated by treatment group.
- In PILLAR and ASPIRE, a logistic regression model, including baseline HCV RNA (continuous parameter) and stratification factors genotype 1 subtype and prior PR response (in ASPIRE only), was used to compare the proportions of patients in each treatment group with SVR at week 72 (PILLAR) and SVR24 (ASPIRE).
- In all included studies, only descriptive statistics were provided for eRVR, relapse, and HRQoL; no statistical analyses of between-group differences were conducted.
- In QUEST-1, QUEST-2, and PROMISE, multiplicity was adjusted by following a specific order, with testing SVR12 first at the 5% significance level followed by testing only SVR24 (secondary end point) if the primary end point was rejected at the 5% significance level. In PILLAR, a closed testing procedure was used to control for multiple comparisons and the overall significance level of 5%. In ASPIRE, multiple comparisons were controlled by comparing results of the simeprevir groups with the same dose (different duration with triple therapy) versus controls at the 2.5% significance level. Groups within dose levels were then compared at the 1.67% significance level only if there was a significant difference against controls.
- In QUEST-1, QUEST-2, and PROMISE, subgroup analyses were performed using a logistic regression model including treatment group, baseline $\log_{10}$ HCV RNA (included as continuous parameter), and the stratification factors genotype 1 subtype and IL28B genotype, in addition to the subgroup parameter. In PILLAR and ASPIRE, subgroup analyses were performed using logistic regression, including baseline HCV RNA (continuous), dose, duration of treatment, and stratification factor (genotype 1 subtype). In PILLAR, treatment groups containing the same dose were pooled with treatment regimens and doses not approved by Health Canada;[1] thus, subgroup results are not presented in this review.
- In QUEST-1, QUEST-2, and PROMISE, FSS and WPAI were analyzed using a piecewise-linear mixed model to compare the area under the curve (AUC) from baseline to week 60 between the simeprevir and the placebo treatment groups.
- Depression severity with the CES-D was analyzed descriptively at Weeks 4, 12, 24, 36, 48, 60, and 72.

a) Analysis Populations

In all studies, the following data sets were defined:

Full Analysis Set (FAS): all patients randomized to receive study medication (simeprevir and placebo). The FAS was the primary population for all analyses.

Safety Analysis Set (SAS): the SAS included all patients in the FAS population.

3.3 Patient Disposition

The disposition of patients is presented in Table 11 for the studies of treatment-naive patients and Table 12 for the studies of treatment-experienced patients. Overall study withdrawal was 7.9% in QUEST-1, 7.4% in QUEST-2, and 6.1% in PROMISE. Among the treatment groups using Health Canada–approved doses, overall study withdrawal was 8.4% in PILLAR and 9.1% in ASPIRE. A greater proportion of patients in the placebo groups, compared with the simeprevir groups, withdrew from the study in QUEST-2 (12.7% versus 4.7%) and in PROMISE (10.5% versus 3.8%). In the studies of treatment-naive patients, the

proportion of patients in the simeprevir groups meeting RGT criteria for shortened treatment duration (24 weeks) ranged from 79.2% to 91.4%, while in PROMISE the proportion of patients in the simeprevir group meeting RGT criteria for shortened treatment was 92.7%.

TABLE 11: PATIENT DISPOSITION FOR STUDIES OF TREATMENT-NAIVE PATIENTS

	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
Screened, N	481		474		506	
Randomized, N	395		393		388	
Discontinued From Study, N (%)	10/130 (7.7)	21/264 (8.0)	17/134 (12.7)	12/257 (4.7)	[redacted]	[redacted]
Lost to follow-up	6 (4.6)	9 (3.4)	6 (4.5)	4 (1.6)	[redacted]	[redacted]
Withdrawal by patient	1 (0.8)	8 (3.0)	5 (3.7)	6 (2.3)	[redacted]	[redacted]
Patient not compliant	1 (0.8)	2(0.8)	1 (0.7)	0	0	0
Entered another trial	0	0	5 (3.7)	0	0	0
AE	0	0	0	2 (0.8)	1 (1.3)	1 (1.3)
Sponsor decision/other	2 (1.5)	2(0.8)	0	0	[redacted]	[redacted]
Completed to week 72, N (%)	28/130 (21.5)	62/264 (23.5)	51/134 (38.1)	111/257 (43.2)	[redacted]	[redacted]
Ongoing from week 60, N (%)	92/130 (70.8)	181/264 (68.6)	66/134 (49.3)	134/257 (52.1)	NA	
Met RGT criteria for short duration of PR therapy	N/A	224/264 (84.8)	N/A	235/257 (91.4)	[redacted]	[redacted]
ITT, N	130	264	134	257	77	77
PP, N	N/A					
Safety, N	130	264	134	257	77	77

AE = adverse event; ITT = intention-to-treat; NA = not applicable; PL = placebo; PP = per-protocol; PR = peginterferon and ribavirin combined therapy; RGT = response-guided therapy; SIM = simeprevir.Source: Clinical Study Reports.[18-20]
Note: Data for the regimens not approved by Health Canada are not reported here.

TABLE 12: PATIENT DISPOSITION FOR STUDIES OF TREATMENT-EXPERIENCED PATIENTS

	ASPIRE		PROMISE	
	PLPR48 (N = 66)	SIM12PR48 (N = 66)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
Screened, N	618		462	
Randomized, N	463		394	
Discontinued from study, n/N (%)	7/66 (10.6)	5/66 (7.6)	14/133 (10.5)	10/260 (3.8)
Lost to follow-up	2 (3.0)	2 (3.0)	3 (2.3)	5 (1.9)
Withdrawal by patient	5 (7.6)	1 (1.5)	10 (7.5)	4 (1.5)
Patient not compliant	0	0	0	0
Entered another trial	0	0	0	0
AE	0	1 (1.5)	0	1 (0.4)
Sponsor decision/ other	0	1 (1.5)	1 (0.8)	0
Completed to week 72, n/N (%)	59/66 (89.4)	61/66 (92.4)	57/133 (42.9)	127/260 (48.8)
Ongoing from week 60, n/N (%)	NA		62/133 (46.6)	123/260 (47.3)
Met RGT criteria for short duration of PR therapy	NA		NA	241/260 (92.7)
ITT, N	66	66	133	260
PP, N	NA		NA	
Safety, N	66	66	133	260

AE = adverse event; ITT = intention-to-treat; NA = not applicable; PL = placebo; PP = per-protocol; PR = peginterferon and ribavirin combined therapy; RGT = response-guided therapy; SIM = simeprevir.Source: Clinical Study Reports.[27,28]
Note: Data for the regimens not approved by Health Canada are not reported here.

3.4 Critical Appraisal

3.4.1 Internal Validity

a) Selection, Allocation, and Disposition of Patients

- All studies were randomized and DB; however, the majority of patients in the QUEST-1, QUEST-2, PILLAR, and PROMISE studies were essentially unblinded after week 24 due to the majority of simeprevir patients meeting RGT criteria for the shortened duration of PR therapy. This would be expected to affect the internal validity of between-treatment comparisons of the more subjective outcomes such as quality of life.
- The studies employed appropriate methods of allocation concealment (central allocation through telephone-based, interactive voice response system). Placebo interventions were identical in appearance to their respective active treatments.
- Baseline characteristics of treatment groups were generally similar, with the exception of the IL28B genotype in ASPIRE and PILLAR. However, the IL28B data were available only for patients who signed the separate informed consent form, so those data were not available for all patients. Thus, it is uncertain whether an imbalance in this patient characteristic existed and, if it did, its impact on the results remains uncertain.
- In all studies, the proportion of patients who withdrew was relatively low and no per-protocol analyses were performed. There were noticeable between-group differences in withdrawal in

QUEST-2 (4.7% versus 12.7%) and in PROMISE (3.8% versus 10.5%) for the simeprevir and placebo groups, respectively, though the differences likely had a minor impact on the findings.
- In ASPIRE, subgroups of prior relapse, prior partial response, and null response were small (n = < 27), and may be insufficiently powered to detect statistically significant differences.

b) Intervention and Comparator
- In all included studies, patients in all groups were treated similarly with regard to other interventions. Specifically, the proportion of patients with dose adjustments for PR was generally similar between-treatment groups.
- Stopping rules employed in the trials (APPENDIX 9: VIROLOGIC STOPPING CRITERIA IN INCLUDED STUDIES) differed between trials and appeared to be less stringent compared with those in the simeprevir product monograph approved by Health Canada.[1] How this may have had an impact on the treatment effect of simeprevir compared with placebo is uncertain.
- In the studies using RGT, the majority of patients in the simeprevir groups qualified for shortened treatment (24 weeks), while placebo patients remained on triple therapy for 48 weeks regardless of response. The difference in the treatment period complicates the interpretation of AE data, given that these data were presented as proportions rather than as rates.

3.4.2 External Validity

[redacted]

- In PILLAR, the exclusion of patients with cirrhosis may have contributed to high SVR rates.
- All included studies excluded patients with HIV coinfection; thus, efficacy with the Health Canada–approved dose of simeprevir among this population remains uncertain.
- In all included studies, patients were only followed for 72 weeks; thus, the long-term effect of therapy on hepatitis-related mortality and morbidity is unknown.
- Trials compared simeprevir triple therapy with PR alone; trials directly comparing simeprevir triple therapy with triple combinations of other DAAs would be informative for current clinical practice.

3.5 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 6). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.5.1 Sustained Virologic Response

SVR12 was the primary outcome in two studies of treatment-naive patients (QUEST-1, and QUEST-2), and one study of treatment-experienced patients (PROMISE). The proportions of treatment-naive patients achieving SVR12 in QUEST-1 and QUEST-2 were 79.5% and 81.3% for simeprevir versus 50.0% and 50.0% for placebo, respectively (Table 13). The proportion of treatment-experienced patients achieving SVR12 in PROMISE was 79.2% for simeprevir and 36.1% for placebo (Table 14). All three studies met their primary outcome, reporting statistically significant between-treatment differences in SVR favouring simeprevir; however, the ARD was approximately 10% higher in the treatment-experienced patients (43.0%) compared with treatment-naive patients (29.3% and 32.2%).

SVR24 was the primary outcome in one study (ASPIRE). The proportion of patients achieving SVR24 in this study of treatment-experienced patients was 66.7% for simeprevir versus 22.7% for placebo. [redacted]

[redacted]Between-treatment differences in SVR24 were reported for the remaining four studies; however, in the case of QUEST-1, QUEST-2, and PROMISE, these results are based on incomplete data, most notably for the placebo groups.

SVR at week 72 was the primary outcome in PILLAR. The proportion of patients achieving SVR at week 72 in this study of treatment-experienced patients was 77.9% for simeprevir versus 64.9% for placebo. The difference was statistically significant in favour of simeprevir, with an ARD of 15.4% (Table 13).

3.5.2 Extended Rapid Virologic Response

The observed proportion of patients achieving eRVR was higher in the simeprevir group than the placebo group in all studies. In the studies of treatment-naive patients, the proportions of patients achieving eRVR ranged from [redacted] with simeprevir, and [redacted] with placebo. In the studies of treatment-experienced patients, the proportion of patients achieving eRVR ranged from 60.6% to 77.6% with simeprevir, and 1.5% to 1.6% with placebo. Statistical analyses of between-treatment differences were not performed. Additional detail regarding eRVR rates are presented in (Table 13 and Table 14)

3.5.3 Relapse

The observed proportion of patients experiencing viral relapse was lower in the simeprevir group than the placebo group in all studies. In the studies of treatment-naive patients, the proportions of patients experiencing viral relapse ranged from [redacted] with simeprevir, and [redacted] with placebo. In the studies of treatment-experienced patients, the proportion of patients experiencing viral relapse ranged from 11.8% to 18.5% with simeprevir, and 44.4% to 48.4% with placebo. Statistical analyses of between-treatment differences were not performed. Additional details regarding relapse rates are presented in (Table 13 and Table 14).

3.5.4 Health-Related Quality of Life

A summary of the EQ-5D VAS change in scores from baseline at weeks 12, 24, 48, and 72 is presented in Table 13 for the studies of treatment-naive patients and in Table 14 for the studies of treatment-experienced patients. Higher scores indicate greater HRQoL. Change from baseline was calculated by subtracting the baseline score from the post-baseline score; therefore, a positive change indicates an improvement in HRQoL, and a negative change indicates a decline or deterioration in HRQoL. A summary of the EQ-5D valuation index change in scores from baseline at weeks 12, 24, 48, and 72 is presented in Table 13 for the studies of treatment-naive patients and in Table 14 for the studies of treatment-experienced patients. Higher scores indicate greater HRQoL. Similar to the VAS, change from baseline was calculated by subtracting the baseline score from the post-baseline score, a positive change suggesting an improvement in HRQoL and a negative change suggesting a decline or deterioration in HRQoL. No statistical analyses of EQ-5D data were conducted.

[redacted]

[redacted]

Data for WPAI was also assessed in phase 3 studies (QUEST-1, QUEST-2, and PROMISE) (see Table 23). Based on the AUC to week 60 for the WPAI scores, simeprevir-treated patients experienced statistically less work productivity and activity impairment compared with placebo in all three trials.

3.5.5 Mortality

In the studies of treatment-naive patients, two deaths were reported in the simeprevir groups (colon cancer and unknown cause), and no deaths were reported in the placebo groups. The investigator considered the death of unknown cause to be likely due to sudden cardiac death. In the studies of treatment-experienced patients, two deaths were reported in the simprevir group (bacterial meningitis/encephalitis and bilateral pneumonia/septic shock) and one death in the placebo group (liver cancer with metastasis to lung). The deaths were deemed unrelated to the study medication (Table 13 and Table 14).

TABLE 13: KEY EFFICACY OUTCOMES FOR STUDIES OF TREATMENT-NAIVE PATIENTS

	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
SVR 12						
n/N (%)	[redacted]	[redacted]	67/134 (50.0)	209/257 (81.3)	51/77 (66.2)	62/77 (80.5)
Adjusted proportion (95% CI)	[redacted]	[redacted]	49.7 (42.0 to 57.3)	81.9 (77.2 to 86.6)	NA	
ARD (95% CI)	[redacted]		32.2 (23.3 to 41.2)		NA	
P value	[redacted]		< 0.001		NA	
SVR 24						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	50/77 (64.9)	62/77 (80.5)
Adjusted proportion (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	NA	
ARD (95% CI)	[redacted]		[redacted]		17.9 (1.7, 34.1)	
P value	[redacted]		[redacted]		0.013	
SVR AT 72 WEEKS						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	50/77 (64.9)	60/77 (77.9)
Adjusted proportion (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	NA	
ARD (95% CI)	[redacted]		[redacted]		15.4 (–1.1 to 32.0)	

	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
P value					0.037	
eRVR						
n/N (%)					4/77 (5.2)	58/77 (75.3)
Relapse						
n/N (%)			21/88 (23.9)		11/62 (17.7)	6/69 (8.7)
EQ-5D VAS						
Mean (SE) at baseline, N						
Mean (SE) change from baseline at week 4, N						
Mean (SE) change from baseline at week 12, N						
Mean (SE) change from baseline at week 24, N						
Mean (SE) change from baseline at week 36, N						
Mean (SE) change from baseline at week 48, N						
Mean (SE) change from baseline at week 60, N						
Mean (SE) change from baseline at week 72, N						
EQ-5D Valuation Index						
Mean (SE) at baseline, (N)						
Mean (SE) change from baseline at week 4, N						
Mean (SE) change from baseline at week 12, N						
Mean (SE) change from baseline at week 24, N						

	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
Mean (SE) change from baseline at week 36, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Mean (SE) change from baseline at week 48, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 60, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Mean (SE) change from baseline at week 72, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality						
N (%)	[redacted]	[redacted]	0	2 (0.8)	0	0

ARD = adjusted risk difference; CI = confidence interval; eRVR = extended rapid virologic response; EQ-5D = EuroQol-5-dimensional scale; N/A = not applicable; PL = placebo; PR = peginterferon and ribavirin combined therapy; RD = risk difference; SE = standard error; SIM = simeprevir; SVR = sustained virologic response; VAS = Visual Analogue Scale.
Source: Clinical Study Reports.[18-20]

TABLE 14: KEY EFFICACY OUTCOMES FOR STUDIES OF TREATMENT-EXPERIENCED PATIENTS

	ASPIRE		PROMISE	
	PLPR48 (N = 66)	SIM12PR48 (N = 66)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
SVR 12				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted proportion (95% CI)	NR		36.6 (28.7 to 44.5)	79.6 (74.8 to 84.4)
ARD (95% CI)	NR		[redacted]	
P value	NR		[redacted]	
SVR 24				
n/N (%)	15/66 (22.7)	44/66 (66.7)	20/64 (31.3)	199/254 (78.3)
Adjusted proportion (95% CI)	[redacted]		31.2 (19.9 to 42.5)	78.3 (73.3 to 83.3)
ARD (95% CI)	[redacted]		47.1 (34.8 to 59.5)	
P value	< 0.001		< 0.001	
SVR at week 72				
n/N (%)			[redacted]	[redacted]
Adjusted proportion (95% CI)			[redacted]	[redacted]
ARD (95% CI)			[redacted]	
P value	NA		[redacted]	
ERVR				
n/N (%)	1/66 (1.5)	40/66 (60.6)	[redacted]	[redacted]
Relapse				
n/N (%)	12/27 (44.4)	6/51 (11.8)	45/93 (48.4)	46/249 (18.5)
EQ-5D VAS				
Mean (SE) at baseline, (N)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 4, N	[redacted]		[redacted]	[redacted]
Mean (SE) change from baseline at week 12, N	[redacted]		[redacted]	[redacted]
Mean (SE) change from baseline at week 24, N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 36, N	[redacted]		[redacted]	[redacted]
Mean (SE) change from baseline at week 48, N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SE) change from baseline at week 60, N	[redacted]		[redacted]	[redacted]
Mean (SE) change from baseline at week 72, N	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D Valuation Index				
Mean (SE) at baseline, (N)	[redacted]	[redacted]	[redacted]	[redacted]

	ASPIRE		PROMISE	
	PLPR48 (N = 66)	SIM12PR48 (N = 66)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
Mean (SE) change from baseline at week 4, N	[redacted]			
Mean (SE) change from baseline at week 12, N	[redacted]			
Mean (SE) change from baseline at week 24, N	[redacted]			
Mean (SE) change from baseline at week 36, N	[redacted]			
Mean (SE) change from baseline at week 48, N	[redacted]			
Mean (SE) change from baseline at week 60, N	[redacted]			
Mean (SE) change from baseline at week 72, N	[redacted]			
Mortality				
n (%)	0	1 (1.5)	1 (0.8)	1 (0.4)

ARD = adjusted risk difference; CI = confidence interval; eRVR = extended rapid virologic response; EQ-5D = EuroQol-5-Dimensions; NA = not applicable; NR = not reported; PL = placebo; PR = peginterferon and ribavirin combined therapy; RD = risk difference; SE = standard error; SIM = simeprevir; SVR = sustained virologic response; VAS = visual analogue scale.

Source: Clinical Study Reports.[27,28]

3.5.6 Subgroup Analyses

Pre-planned analyses of SVR12 and viral relapse by prior response to PR treatment, fibrosis stage, and presence of Q80K polymorphism are presented in Table 17 and Table 18.

a) Prior Response to PR Treatment

Subgroup results based on response to prior PR therapy (relapse, partial, or null) were reported only for the ASPIRE study, given that the PROMISE study exclusively enrolled prior relapsers. In ASPIRE, the proportion of patients achieving [redacted]SVR24 was higher in the simeprevir group compared with placebo in all three subgroups; however, the proportion of simeprevir-treated patients achieving SVR was highest for prior relapsers (76.9%) and lowest for prior null responders (52.9%). Similarly, relapse was less commonly reported among simeprevir-treated patients compared with placebo in all three subgroups.

b) Fibrosis Level

Four trials (QUEST-1, QUEST-2, ASPIRE, and PROMISE) reported subgroup analyses of SVR (12 or 24) based on the fibrosis stage. SVR results were consistent with the main analyses; the proportion of patients achieving SVR was higher in the simeprevir groups compared with placebo across all fibrosis stages. However, patients at more advanced stages of fibrosis were less likely to achieve SVR regardless of treatment. Similarly, relapse was less commonly reported among simeprevir-treated patients

compared with placebo for all fibrosis stages; however, there was a trend toward greater relapse among patients with higher METAVIR fibrosis scores, regardless of treatment.

c) HIV Coinfection

Given that all studies excluded patients with HIV coinfection, subgroup analyses were not performed for this subgroup of interest.

d) Q80K Genotype Mutation

The phase 3 trials (QUEST-1, QUEST-2 and PROMISE) reported subgroup analyses of SVR 12 by Q80K genotype mutation in both HCV genotype 1a- and 1b-infected patients. As seen in Table 19, the proportion of simeprevir-treated patients achieving SVR12 was higher for patients with genotype 1a virus lacking the Q80K mutation. Though no statistical analyses were performed, between-treatment differences favouring simeprevir were numerically greater among patients without the Q80K genotype mutation. The Q80k genotype mutation was nearly non-existent in the genotype 1b virus.

3.6 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

For all trials, the proportions of patients experiencing AEs were reported both for (1) the initial 12 weeks of treatment, and (2) the "treatment period." Of note, except for the ASPIRE study in which the treatment period was a standard duration (48 weeks) for both treatment groups, the interpretation of the AE data by treatment period is complicated by the large proportion of simeprevir-treated patients that qualified for shorter-duration treatment.

3.6.1 Serious Adverse Events

Based on data reported for the treatment period, the proportion of patients experiencing at least one SAE was greater in the placebo groups compared with the simeprevir groups (QUEST-1, [redacted] versus [redacted]; QUEST-2, [redacted] versus [redacted]; PILLAR, 13.0% versus 5.2%; PROMISE: 7.5% versus 5.4% [Table 15 and Table 16]). However, in ASPIRE the proportion of patients who experienced at least one SAE was greater in the simeprevir group compared with the placebo group (10.6% versus 6.1%). Between-treatment differences based on the initial 12 weeks of treatment were less apparent and were numerically larger in the placebo groups in only two studies (QUEST-1, 3.8% versus 2.7%; PROMISE, 2.3% versus 1.2%). During the initial 12 weeks of treatment, SAEs observed in the simeprevir groups included syncope, major depression, infections and infestations, diarrhea, vomiting, skin and subcutaneous tissue disorders, and photosensitivity reactions.

3.6.2. Adverse Events

The majority of patients (> 90%) in all treatment groups reported at least one AE during the initial 12 weeks of treatment; frequencies reported for the treatment period were ≥ 94%. In all studies, the most commonly reported AEs were fatigue, headache, and infections and infestations (Table 15, Table 16, Table 20, and Table 21).

3.6.3 Withdrawals due to Adverse Events (WDAEs)

The percentage of patients who withdrew due to AEs was < 2% across all studies and treatment groups.

3.6.4 Notable Harms

The CDR reviewers, in discussion with the clinical expert involved in the review, identified a priori several AEs of interest: rash, fatigue, anemia, neutropenia, pruritus, depression, insomnia, nausea, gastrointestinal complications, and photosensitivity. Additional details regarding notable harms during the treatment period are presented in (Table 15 and Table 16), and during the initial 12 weeks of treatment in (Table 20 and Table 21).

Data for two of the harms of interest, fatigue and depression, were also assessed in phase 3 studies (QUEST-1, QUEST-2, and PROMISE), using the FSS and CES-D respectively (see Table 22). Based on the AUC to week 60 for the FSS scores, simeprevir-treated patients experienced statistically less fatigue compared with placebo-treated patients in all three trials. CES-D scores were not noticeably different between simeprevir and placebo groups at time points up to week 24, but there was a trend toward lower (more favourable) depression scores in the simeprevir groups compared with the placebo groups at weeks 36 and 48. The CES-D was an exploratory outcome and no statistical testing of these data was conducted.

TABLE 15: HARMS FOR STUDIES OF TREATMENT-NAIVE PATIENTS DURING THE ENTIRE TREATMENT DURATION

	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
AEs						
Patients with > 0 AEs, n (%)	125 (96.2)	255 (96.6)	[redacted]	[redacted]	75 (97.4)	76 (98.7)
Most common AEs, n (%)[a]						
fatigue	53 (40.8)	110 (41.7)	[redacted]	[redacted]	37 (48.1)	32 (41.6)
headache	51 (39.2)	88 (33.3)	[redacted]	[redacted]	40 (51.9)	35 (45.5)
infections and infestations	43 (33.1)	71 (26.9)	[redacted]	[redacted]	32 (41.6)	23 (29.9)
SAEs						
Patients with > 0 SAEs, n (%)	8 (6.2)	10 (3.8)	[redacted]	[redacted]	10 (13.0)	4 (5.2)
WDAEs						
WDAEs, n (%)	0	0	[redacted]	[redacted]	1 (1.3)	1 (1.3)
AEs Leading to Permanent Stop of Study Treatment (SIM/PL)						
N (%)	4 (3.1)	9 (3.4)	[redacted]	[redacted]	2 (2.6)	3 (3.9)
Notable Harms[a]						
rash	[redacted]	[redacted]	[redacted]	[redacted]	18 (23.4)	16 (20.8)
fatigue	[redacted]	[redacted]	[redacted]	[redacted]	37 (48.1)	32 (41.6)
anemia	[redacted]	[redacted]	[redacted]	[redacted]	16 (20.8)	17 (22.1)

	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	16 (20.8)	19 (24.7)
pruritus	[redacted]	[redacted]	[redacted]	[redacted]	35 (45.5)	30 (39.0)
depression	[redacted]	[redacted]	[redacted]	[redacted]	14 (18.2)	9 (11.7)
insomnia (sleep loss)	[redacted]	[redacted]	[redacted]	[redacted]	23 (29.9)	23 (29.9)
nausea	[redacted]	[redacted]	[redacted]	[redacted]	21 (27.3)	20 (26.0)
diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	12 (15.6)	11 (14.3)
vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
photosensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; PL = placebo; PR = peginterferon and ribavirin combined therapy; SAE = serious adverse event; SIM = simeprevir; WDAE = withdrawal due to adverse event.

[a] Frequency > 5% during the entire treatment period in QUEST-1 and QUEST-2, > 10% during the entire treatment period in PILLAR.

[b] Number of patients with > 0 Grade 3 or 4 AEs during the entire treatment period.

[c] Number of patients with > 0 AEs during the entire treatment period.

Source: Clinical Study Reports.[18-20]

TABLE 16: HARMS FOR STUDIES OF TREATMENT-EXPERIENCED PATIENTS DURING THE ENTIRE TREATMENT DURATION

	ASPIRE		PROMISE	
	PLPR48 (N = 66)	SIM12PR48 (N = 66)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
AEs				
Patients with > 0 AEs, n (%)	[redacted]	[redacted]	125 (94.0)	253 (97.3)
Most common AEs [a], n (%)				
fatigue	29 (43.9)	26 (39.4)	58 (43.6)	84 (32.3)
headache	24 (36.4)	29 (43.9)	48 (36.1)	86 (33.1)
infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
SAEs				
Patients with > 0 SAEs, N (%)	4 (6.1)	7 (10.6)	10 (7.5)	14 (5.4)
WDAEs				
WDAEs, N (%)	0	1 (1.5)	0	1 (0.4)
AEs Leading to Permanent Stop of Study Treatment (SIM/PL)				
N (%)	3 (4.5)	4 (6.1)	0	0
Notable Harms [a]				
rash	9 (13.6)	10 (15.2)	30 (22.6)	60 (23.1)
fatigue	29 (43.9)	26 (39.4)	58 (43.6)	84 (32.3)
anemia	13 (19.7)	10 (15.2)	27 (20.3)	44 (16.9)
neutropenia	11 (16.7)	18 (27.3)	29 (21.8)	46 (17.7)
pruritus	11 (16.7)	20 (30.3)	37 (27.8)	72 (27.7)
depression	[redacted]	[redacted]	[redacted]	[redacted]
insomnia (sleep loss)	[redacted]	[redacted]	[redacted]	[redacted]
nausea	[redacted]	[redacted]	[redacted]	[redacted]
diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
vomiting	[redacted]	[redacted]	[redacted]	[redacted]
photosensitivity	[redacted]	[redacted]	0 [b]	9 (3.5) [b]

AE = adverse event; PL = placebo; PR = peginterferon and ribavirin combined therapy; SAE = serious adverse event; SIM = simeprevir; WDAE = withdrawal due to adverse event.

[a] Frequency > 5% during the entire treatment period.
[b] Number of patients with > 0 AEs during the entire treatment period.
Source: Clinical Study Reports.[27,28]

4. DISCUSSION

4.1 Summary of Available Evidence

A total of five DB RCT comparing simeprevir with placebo (both in combination with PR) in adults with genotype 1 CHC were included in the systematic review. Three of the five studies (QUEST-1 [n = 395], QUEST-2 [n = 393], and PILLAR [n = 386]) were conducted with patients who were treatment-naive and two studies were conducted with patients who were treatment-experienced (ASPIRE [n = 463] and PROMISE [n = 393]). In ASPIRE, treatment-experienced patients consisted of null responders, partial responders, and relapsers following at least one course of PR therapy, while all patients in PROMISE had relapsed after following at least one course of PR therapy. No active comparator trials were identified by CADTH.

4.2 Interpretation of Results

4.2.1 Efficacy

SVR is considered to represent complete elimination of HCV, and is the goal of treatment in CHC. In all five included trials, simeprevir, in combination with PR, resulted in a statistically significantly greater proportion of patients achieving SVR12 and/or SVR24 compared with PR therapy alone. The clinical expert consulted for this review considered that the SVR12 and SVR24 were relatively high among the placebo groups in the studies of treatment-naive patients compared with what is seen in clinical practice, and noted that this may be a consequence of the select patient population and restrictive exclusion criteria.

SVR24 data for three trials (QUEST-1, QUEST-2, and PROMISE) are based on week-60 interim analyses and should be interpreted with caution, given that a much larger proportion of simeprevir-treated patients was able to be assessed 24 weeks after the end of treatment compared with placebo-treated patients (placebo-treated patients were not eligible for shortened treatment duration and thus were less likely to have been off treatment for 24 weeks at the data cut-off). However, SVR12 has been shown to be highly correlated with SVR24 (Center for Drug Evaluation and Research, Food and Drug Administration [FDA][23]), and regulatory bodies have accepted SVR as a primary outcome (see APPENDIX 5: VALIDITY OF OUTCOME MEASURES)

The magnitude of the differential effect of simeprevir compared with placebo was greater among treatment-experienced patients compared with treatment-naive patients, due to the poor response to PR therapy in previously treated patients. The manufacturer-conducted subgroup analyses suggest that simeprevir plus PR, compared with PR alone, results in a higher likelihood of achieving SVR regardless of METAVIR scores or response to previous PR therapy. However, the likelihood of achieving SVR appears to be lower in patients with higher METAVIR fibrosis scores compared with lower scores, and in prior null responders to PR compared with those with relapse subsequent to PR.

In all studies, the addition of simeprevir to PR therapy resulted in a lower proportion of patients experiencing viral relapse. According to the clinical expert, results for relapse were reflective of what is usually seen in clinical practice when patients are treated with DAAs. [redacted] In the treatment-naive studies, the relapse rate in the simeprevir with combined PR therapy groups ranged from [redacted]. The relapse rate in ASPIRE (11.8%) was marginally lower than what is typically seen in treatment-experienced patients. The relapse rate in the simeprevir group in PROMISE

(18.5%) concurred with typical relapse rates in treatment-experienced patients receiving DAAs. Both eRVR and relapse were measured descriptively, with no statistical analyses performed.

Although the EQ-5D is a generic quality-of-life instrument with uncertainty regarding the minimal clinically important difference for patients with CHC, it does appear to be responsive to the effects of treatment for CHC.[29] Overall, the EQ-5D results suggest that the addition of simeprevir does not add to the HRQoL burden of treatment for CHC, given that the between-treatment differences on the 100-point VAS score were of a magnitude of only 2 to 3 points at week 12. In both the VAS and valuation index scores, more noticeable between-treatment differences (suggesting more favourable HRQoL in the simeprevir group) were not apparent until week 36. These results should be interpreted with caution for the following reasons: patients' knowledge of their treatment status (based on continuation of treatment beyond 24 weeks) may have influenced their responses, the clinical importance of the between-treatment differences is unclear, and no statistical analyses were performed in the individual studies reporting these data. In the phase 3 studies, analyses were performed when all randomized patients had completed their week 60 visits or had discontinued earlier; thus, data were limited at the 72-week time point. At the time when this report was written, end-of-treatment data at 72 weeks was available only from less than half of the population. Although the conclusions that can be drawn from the analysis at 72 weeks are limited, these concerns are mitigated, as the interim 60-week analysis was pre-specified as per International Conference on Harmonisation standards in the study protocol and the defined primary analysis occurred at the time point when the primary end point (SVR12) would have been met for all patients enrolled. Work productivity and activity impairment, as measured by the AUC to week 60 using the WPAI, was statistically significantly less in simeprevir groups compared with placebo groups in the three phase 3 trials; however, the clinical importance of this difference is uncertain.

Mortality was rare in all studies, and the manufacturer considered these deaths unrelated to simeprevir. As expected, the included studies were too short in duration to assess the complications of CHC infection such as mortality and hepatic-related morbidity (mainly cirrhosis and hepatocellular carcinoma).

Subgroup data from QUEST-1, QUEST-2, and PROMISE suggest that, among patients treated with simeprevir, Q80K polymorphism in HCV genotype 1a is associated with a lower likelihood of achieving SVR compared with HCV genotype 1a without Q80k polymorphism. In addition, results from the manufacturer's NMA suggest that simeprevir is inferior to boceprevir and telaprevir in terms of SVR in patients with genotype 1a Q80K polymorphism. According to the clinical expert, the Q80K genotype mutation is a specific mutation that affects patients with genotype 1a HCV, and is important for treatment with simeprevir, but not with other DAAs such as boceprevir and telaprevir. As noted by the expert, the Q80K mutation is present in between 40% and 50% of patients in North America with the genotype 1a infection. The Health Canada product monograph[1] indicates that when accessible, testing for Q80K can be considered in patients with genotype 1a HCV. The clinical expert felt that genotype 1a patients should not receive simeprevir unless they have this test result available. According to the manufacturer, testing for Q80K is available as of February 16, 2014 through the BC Centre for Excellence Research Laboratory; it is also currently available through the Laboratoire Public Santé du Quebec. The cost of testing all samples through the BC Centre for Excellence Research Laboratory will be covered by Janssen Canada. A CADTH report found no information on the diagnostic accuracy of laboratory tests for the identification of Q80K polymorphism in patients with HCV genotype 1.[30]

Given that all studies excluded patients with HIV coinfection, subgroup analyses were not performed for this subgroup of interest. Patients with HIV coinfection is an important subpopulation of interest, as the presence of HIV has been shown to accelerate the natural history of HCV infection, specifically regarding cirrhosis and end-stage liver disease.[22]

Without head-to-head trial data for simeprevir versus other DAAs, the manufacturer conducted a Bayesian NMA based on a systematic review of RCTs to compare simeprevir with telaprevir and boceprevir, all in combination with PR (APPENDIX 6: SUMMARY OF CRICITAL APPRAISAL OF THE NETWORK META-ANALYSIS). No significant differences in efficacy between simeprevir and either telaprevir or boceprevir were identified, although results suggest that simeprevir may provide some advantages in terms of reduced harms. Another DAA, sofosbuvir, not included in the NMA but recently approved in Canada, has been shown to be effective for the treatment of patients with genotype 1 HCV (APPENDIX 8: OVERVIEW OF SAFETY AND EFFICACY OF SOFOSBUVIR). Sofosbuvir was not included in the manufacturer's NMA. Given a number of limitations with the NMA and the lack of head-to-head trials, the comparative efficacy and safety of the DAAs should be considered uncertain.

4.2.2 Harms

The overall safety results in all included studies revealed (during the overall treatment duration and first 12 weeks) a generally similar incidence of AEs, with the exception of increased neutropenia, pruritus, nausea, and photosensitivity during the first 12 weeks of treatment in the simeprevir group (Table 20 and Table 21). Notable harms identified by the patient input summary included fatigue, insomnia, nausea, and headaches, all of which were generally similar between-treatment groups, with the exception of a greater proportion of patients in the simeprevir group experiencing nausea in most studies during the entire treatment phase. Fatigue, measured as by the AUC to week 60 using the FSS was statistically significantly less in simeprevir groups compared with placebo in the three phase 3 trials; however, the clinical importance of this difference is uncertain. Rash, pruritus, anemia, neutropenia, and photosensitivity are frequently observed with other similar class molecules (Center for Drug Evaluation and Research, FDA[23]). During the entire treatment period, the proportion of patients having an SAE was higher in the placebo groups (with the exception of the ASPIRE study); however, interpreting these findings is complicated by differences in treatment duration between the groups. Anemia, identified as one of the most notable AEs of interest by the clinical expert, did not increase with treatment with simeprevir. In all studies, investigators controlled for anemia by reducing the ribavirin dose, as the use of erythropoietin was not permitted.

5. CONCLUSIONS

In five DB RCTs, the proportion of treatment-naive (three trials) and treatment-experienced patients (two trials) that achieved SVR was statistically significantly higher among those treated with simeprevir plus PR compared with PR alone. In four of five trials, the simeprevir treatment regimen was based on RGT, and ≥ 79% of patients qualified for the shortened (24-week) duration of treatment. No statistical analyses of between-treatment differences were conducted for other reported efficacy outcomes, including relapse or HRQoL. The trials were of too short a duration to examine between-treatment differences in hepatic morbidity or mortality. Subgroup analyses revealed that simeprevir-treated patients with the genotype 1a Q80k mutation were less likely to achieve SVR compared with those lacking the mutation. The Health Canada–approved monograph for simeprevir indicates that testing for Q80K polymorphism in patients with HCV genotype 1a could be considered when accessible.

Based on the results of the five RCTs, compared with PR therapy alone, patients treated with simeprevir plus PR had an increased incidence of neutropenia, pruritus, nausea, and photosensitivity during the first 12 weeks of treatment. No active comparator RCTs employing Health Canada–approved regimens of simeprevir were identified; thus, the comparative efficacy and safety of simeprevir versus other DAAs approved for the treatment of genotype 1 CHC is uncertain.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) 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 Janssen and other pharmaceutical companies. The chairman of CLF has received honoraria from pharmaceutical companies, including Janssen.

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

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, prevention education, and encouraging testing among at-risk groups. HepCBC received funding from pharmaceutical companies, including Janssen, to support their educational activities, and the author of this report 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 of, exposed to, or concerned about HCV. The Pacific Hepatitis C Network has received no financial support from the pharmaceutical industry. The network declared no conflicts of interest in the preparation of this submission.

The Gastrointestinal (GI) Society is a Canadian charitable organization committed to improving lives of people with GI and liver diseases through providing evidence-based information, organizing support groups, supporting research, advocating access to care, and promoting GI health. The GI Society has received charitable donations, grants, or sponsorships from Janssen and other pharmaceutical companies. It declared no conflicts of interest in the preparation of its submission.

2. Condition and Current Therapy-Related Information

The following information was collected through online surveys or interviews with Canadian patients, caregivers, and health care professionals, and through 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 they 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, the fear of spreading the infection, and the uncertainty about 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 reliance 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 a buildup 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/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 the 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 shouldering 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 for genotype 1 HCV is 24 to 48 weeks of PR, with or without boceprevir or telaprevir. Dual therapy involves weekly injections of peginterferon plus 6 to 8 ribavirin pills per day. Adverse effects can be severe and debilitating, affecting patients' work, families, and mental health. 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 ~75% for some patient groups; however, rates are lower for patients who failed previous therapy. Their addition increases the risk of AEs, particularly rash and anemia, and increases the pill burden by 6 to 12 pills per day. Many patients cannot tolerate treatment, and they 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 the eligibility criteria are denied treatment through provincial drug plans or must wait for treatment until they show serious liver damage. If a patient is denied treatment for HCV because he or she cannot afford it, the increased health problems from the disease are not only a burden on the patient and his or her family (physical, family, or social burden), but they also have an economic burden on the health care system itself, as patients require additional treatments (e.g., liver transplants or other ongoing expensive treatments).

3. Related Information About the Drug Being Reviewed

Although simeprevir still requires concurrent treatment with peginterferon and ribavirin, patients believe simeprevir offers advantages due to its shorter treatment duration (24 weeks for many patients), easier administration (once daily dosing with few food restrictions), decreased side effects compared with boceprevir and telaprevir, and effectiveness in harder-to-treat patients such as those who have failed previous interferon-ribavirin 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 AEs associated with these agents.

Patients treated with simeprevir reported that the 24-week therapy was easier to take than boceprevir or telaprevir, and that they experienced few adverse effects beyond those of peginterferon and ribavirin.

4. Additional Information

One patient group raised concerns that access delays may occur for people living with HIV/HCV coinfection due to the lack of completed phase 3 clinical trials in this population. The group suggested that CDEC consider interim data on simeprevir in the coinfected population, as was done with boceprevir and telaprevir.

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 to 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:	December 19, 2013
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

#	SEARCHES
1	(simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos* or Olysio* or Sovriad*).ti,ab,ot,sh,hw,rn,nm.
2	(923604-59-5 or 9WS5RD66HZ).rn,nm.
3	or/1-2
4	3 use pmez
5	(simeprevir* or TMC435 or TMC 435 or TMC435350 or TMC 435350 or Galexos* or Olysio* or Sovriad*).ti,ab.
6	*simeprevir/
7	or/5-6
8	7 not conference abstract.pt.
9	8 use oemezd
10	4 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:	December 2013
Keywords:	Hepatitis C, simeprevir, Galexos and Olysio.
Limits:	No date limit, English only

Relevant websites from the following sections of the CADTH 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

There were no excluded studies.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 17: SUBGROUP ANALYSES FOR STUDIES OF TREATMENT-NAIVE PATIENTS

	QUEST 1		QUEST 2	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)
SVR 12 WEEKS				
METAVIR Fibrosis Score, n/N (%)				
F0-F1	[redacted]	[redacted]	[redacted]	[redacted]
F2	[redacted]	[redacted]	[redacted]	[redacted]
F3	[redacted]	[redacted]	[redacted]	[redacted]
ARD (95% CI) [a] *P* value	[redacted]		[redacted]	
F4	[redacted]	[redacted]	[redacted]	[redacted]
ARD (95% CI) [a] *P* value	[redacted]		[redacted]	
F0-F2	[redacted]	[redacted]	[redacted]	[redacted]
ARD (95% CI) [a] *P* value	[redacted]		[redacted]	
F3-F4	[redacted]	[redacted]	[redacted]	[redacted]
ARD (95% CI) [a] *P* value	[redacted]		[redacted]	

ARD = adjusted risk difference; CI = confidence interval; PL = placebo; PR = peginterferon and ribavirin combined therapy; SIM = simeprevir; SVR = sustained virologic response.

[a] Derived using logistic regression model including treatment, baseline $\log_{10}$ HCV RNA (included as continuous parameter), and the stratification factors genotype 1 subtype and IL28B genotype.

Source: Clinical Study Reports.[19,20]

TABLE 18: SUBGROUP ANALYSES FOR STUDIES OF TREATMENT-EXPERIENCED PATIENTS

	ASPIRE		PROMISE	
	PLPR48 (N = 66)	SIM12PR48 (N = 66)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
SVR 12 WEEKS				
METAVIR fibrosis score, n/N (%)				
F0-F1	[redacted]	[redacted]	[redacted]	[redacted]
F2	[redacted]	[redacted]	[redacted]	[redacted]
F3	[redacted]	[redacted]	3/15 (20.0)	32/44 (72.7)
ARD (95% CI) [a] *P* value	[redacted]		51.3 (41.4 to 61.6) < 0.001	
F4	[redacted]	[redacted]	5/19 (26.3)	29/39 (74.4)
ARD (95% CI)[a] *P* value	[redacted]		51.6 (41.5 to 61.6) < 0.001	
F0-F2	[redacted]	[redacted]	40/98 (40.8)	137/167 (82.0)
ARD (95% CI)[a] *P* value	[redacted]		49.9 (39.6 to 60.3) < 0.001	
F3-F4	[redacted]	[redacted]	8/34 (23.5)	61/83 (73.5)
ARD (95% CI)[a] *P* value	[redacted]		51.4 (41.5 to 61.3) < 0.001	
Prior Response to PR Therapy, n/N (%)				
Null Responder	[redacted]	[redacted]	NA	
Partial Responder	[redacted]	[redacted]		
Relapser	[redacted]	[redacted]		
SVR 24 Weeks				
METAVIR Fibrosis Score, n/N (%)				
F0-F1	[redacted]	[redacted]	NR	
F2	[redacted]	[redacted]		
F3	[redacted]	[redacted]		
F4	[redacted]	[redacted]		
F0-F2	[redacted]	[redacted]		
F3-F4	[redacted]	[redacted]		
Prior Response to PR Therapy, n/N (%)				
Null Responder	[redacted]	[redacted]	NA	
Partial Responder	[redacted]	[redacted]		
Relapser	[redacted]	[redacted]		

ARD = adjusted risk difference; CI = confidence interval; NA = not applicable; NR = not reported; PL = placebo; PR = peginterferon and ribavirin combined therapy; SIM = simeprevir; SVR = sustained virologic response;
[a] Derived using logistic regression model including treatment, baseline $\log_{10}$ HCV RNA (included as continuous parameter), and the stratification factors genotype 1 subtype and IL28B genotype.
Source: Clinical Study Reports.[27,28]

TABLE 19: SUBGROUP ANALYSES FOR SVR12 BY Q80K GENOTYPE MUTATION AND HCV GENOTYPE

	QUEST-1		QUEST-2		PROMISE	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/ 48 (N = 257)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
SVR 12 Weeks						
HCV Genotype						
Genotype 1a						
n/N (%)	[redacted]				15/54 (27.8)	78/111 (70.3)
Adjusted proportion (95% CI)	[redacted]				21.2 (10.0 to 32.5)	70.5 (60.5 to 80.4)
ARD (95% CI)	[redacted]				49.2 (34.8 to 63.7)	
Q80K n/N (%)	[redacted]				6/20 (30.0)	14/30 (46.7)
No Q80K n/N (%)	[redacted]				9/34 (26.5)	62/79 (78.5)
Genotype 1b						
n/N (%)	[redacted]				34/79 (43.0)	128/149 (85.9)
Adjusted proportion (95% CI)	[redacted]				41.1 (28.6 to 53.5)	85.9 (79.8 to 92.1)
ARD (95% CI)	[redacted]				44.9 (31.6 to 58.2)	
Q80K n/N (%)	[redacted]				0	1/1 (100.0)
No Q80K n/N (%)	[redacted]				34/79 (43.0)	126/147 (85.7)

ARD = adjusted risk difference; HCV = hepatitis C; PL = placebo; PR = peginterferon and ribavirin combined therapy; SIM = simeprevir; SVR = sustained virologic response.

TABLE 20: HARMS FOR STUDIES OF TREATMENT-NAIVE PATIENTS DURING FIRST 12 WEEKS OF TREATMENT

	QUEST-1		QUEST-2		PILLAR	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 77)	SIM12PR24/48 (N = 77)
AEs						
Patients with > 0 AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	74 (96.1)	76 (98.7)
Most common AEs[a], n (%)						
fatigue	[redacted]	[redacted]	[redacted]	[redacted]	NR	
headache	[redacted]	[redacted]	[redacted]	[redacted]		
infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]		
SAEs						
Patients with > 0 SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	7 (9.1)	NR
WDAEs						
WDAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	1 (1.3)	1 (1.3)
AEs Leading to Permanent Stop of Study Treatment (Simeprevir/Placebo)						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	
Notable Harms[a]						
rash	[redacted]	[redacted]	[redacted]	[redacted]	NR	
fatigue	[redacted]	[redacted]	[redacted]	[redacted]		
anemia	[redacted]	[redacted]	[redacted]	[redacted]		
neutropenia	[redacted]	[redacted]	[redacted]	[redacted]		
pruritus	[redacted]	[redacted]	[redacted]	[redacted]		
depression	[redacted]	[redacted]	[redacted]	[redacted]		
insomnia (sleep loss)	[redacted]	[redacted]	[redacted]	[redacted]		
nausea	[redacted]	[redacted]	[redacted]	[redacted]		
diarrhea	[redacted]	[redacted]	[redacted]	[redacted]		
vomiting	[redacted]	[redacted]	[redacted]	[redacted]		
photosensitivity[b]	[redacted]	[redacted]	[redacted]	[redacted]		

AE = adverse event; PL = placebo; PR = peginterferon and ribavirin combined therapy; SAE = serious adverse event; SIM = simeprevir; WDAE = withdrawal due to adverse event.

[a] Frequency > 5% during the entire treatment period in QUEST-1 and QUEST-2, > 10% during the entire treatment period in PILLAR.

[b] Number of patients with > 0 Grade 3 or 4 AEs during the entire treatment period.

[c] Number of patients with > 0 AEs during the entire treatment period.

Source: Clinical Study Reports.[18-20]

TABLE 21: HARMS FOR STUDIES OF TREATMENT-EXPERIENCED PATIENTS DURING FIRST 12 WEEKS OF TREATMENT

	ASPIRE		PROMISE	
	PLPR48 (N = 66)	SIM12PR48 (N = 66)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
AEs				
Patients with > 0 AEs, n (%)	[redacted]	[redacted]	123 (92.5)	248 (95.4)
Most common AEs[a], n (%)				
fatigue	[redacted]	[redacted]	56 (42.1)	83 (31.9)
headache	[redacted]	[redacted]	48 (36.1)	83 (31.9)
infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	3 (2.3)	3 (1.2)
WDAEs				
WDAEs, n (%)	[redacted]	[redacted]	0	1 (0.4)
AEs LEADING TO PERMANENT STOP OF STUDY TREATMENT (SIMEPREVIR /PLACEBO)				
[redacted]	[redacted]	[redacted]	0	1 (0.4)
NOTABLE HARMS[a]				
rash	[redacted]	[redacted]	19 (14.3)	48 (18.5)
fatigue	[redacted]	[redacted]	56 (42.1)	83 (31.9)
anemia	[redacted]	[redacted]	8 (6.0)	28 (10.8)
neutropenia	[redacted]	[redacted]	22 (16.5)	38 (14.6)
pruritus	[redacted]	[redacted]	22 (16.5)	61 (23.5)
depression	[redacted]	[redacted]	[redacted]	[redacted]
insomnia (sleep loss)	[redacted]	[redacted]	[redacted]	[redacted]
nausea	[redacted]	[redacted]	[redacted]	[redacted]
diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
vomiting	[redacted]	[redacted]	[redacted]	[redacted]
photosensitivity[b]	[redacted]	[redacted]	0	9 (3.5)

AE = adverse event; PL = placebo; PR = peginterferon and ribavirin combined therapy; SAE = serious adverse event; SIM = simeprevir; WDAE = withdrawal due to adverse event.

[a] Frequency > 5% during the entire treatment period.

[b] Number of patients with > 0 AEs during the entire treatment period.

Source: Clinical Study Reports.[27,28]

TABLE 22: FATIGUE AND DEPRESSION SCORES IN PHASE 3 STUDIES

	QUEST-1		QUEST-2		PROMISE	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	PLPR48 (N = 134)	SIM12PR24/48 (N = 257)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
FSS AUC_{60}						
LS Mean (95% CI), N	235.5 (224.1 to 247.0) N = 130	214.9 (205.8 to 223.9) N = 260	225.0 (213.6 to 236.4) N = 133	208.4 (199.4 to 217.3) N = 256	253.0 (241.7 to 264.2) N = 130	226.1 (217.3 to 234.9) N = 257
Difference vs. PL (95% CI) *P* value	–20.7 (–32.7 to –8.6) < 0.001		–16.7 (–29.1 to –4.3) 0.009		–26.9 (–39.1 to –14.7) < 0.001	
CES-D Total Score						
Mean (SE) at baseline (N)	15.5 (0.62) N = 130	15.2 (0.47) N = 261	14.4 (0.66) N = 132	15.1 (0.48) N = 254	13.2 (0.58) N = 130	14.4 (0.42) N = 250
Mean (SE) change from baseline at week 4, N	2.6 (0.61) N = 130	3.8 (0.50) N = 253	4.5 (0.84) N = 129	4.1 (0.43) N = 250	4.0 (0.62) N = 125	3.3 (0.44) N = 248
Mean (SE) change from baseline at week 12, N	3.4 (0.71) N = 127	4.2 (0.56) N = 250	5.1 (0.79) N = 126	5.0 (0.51) N = 242	5.6 (0.71) N = 121	4.2 (0.48) N = 239
Mean (SE) change from baseline at week 24, N	2.9 (0.70) N = 118	3.8 (0.59) N = 249	4.6 (0.93) N = 121	5.1 (0.53) N = 237	4.7 (0.73) N = 116	5.3 (0.55) N = 230
Mean (SE) change from baseline at week 36, N	2.2 (0.71) N = 115	0.5 (0.50) N = 242	4.2 (1.01) N = 114	0.4 (0.51) N = 234	5.0 (0.73) N = 111	1.0 (0.46) N = 232
Mean (SE) change from baseline at week 48, N	3.8 (0.69) N = 115	0.3 (0.52) N = 233	3.6 (0.98) N = 111	–0.1 (0.48) N = 233	6.1 (0.80) N = 114	0.6 (0.46) N = 228
Mean (SE) change from baseline at week 60, N	1.5 (0.74) N = 1 19	0.3 (0.51) N = 238	–0.4 (0.84) N = 115	–1.0 (0.49) N = 233	1.3 (0.74) N = 109	0.1 (0.42) N = 228
Mean (SE) change from baseline at week 72, N	–0.7 (1.61) N = 27	1.1 (0.91) N = 62	1.0 (1.26) N = 52	–0.5 (0.81) N = 108	0.6 (0.90) N = 53	1.4 (0.78) N = 125

AUC_{60} = area under the curve; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; FSS = Fatigue Severity Score; LS = least-squares; PL = placebo; PR = peginterferon and ribavirin combined therapy; SE = standard error; SIM = simeprevir; vs. = versus.

Note: The FSS score ranges from 1 to 7, with higher scores indicating a worse outcome. The AUC_{60} for FSS over time from baseline to week 60 was derived from a piecewise-linear model, allowing the slopes to change at weeks 4, 12, 24, 36, and 48. The CES-D scores range from 0 to 60, with higher scores indicating worse outcome.

TABLE 23: WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT SCORES IN PHASE 3 STUDIES

	QUEST-1		QUEST-2		PROMISE	
	PLPR48 (N = 130)	SIM12PR24/48 (N = 264)	%	SIM12PR24/48 (N = 257)	PLPR48 (N = 133)	SIM12PR24/48 (N = 260)
WPAI Score AUC_{60}						
LS Mean (95% CI), N	1791.2 (1604.4,1978.1) N = 130	1555.4 (1415.9 to 1694.9) N = 260	1909.0 (1726.1 to 2092.0) N = 133	1626.7 (1487.7 to 1765.6) N = 256	2228.0 (2040.8 to 2415.3) N = 130	1680.1 (1534.5 to1825.8) N = 257
Difference vs. PL (95% CI) *P* value	–235.9 (–448.3 to –23.4) 0.030		–282.4 (–491.5 to –73.2) 0.008		–547.9 (–751.9 to –343.9) < 0.001	

AUC_{60} = area under the curve; CI = confidence interval; LS = least-squares; PL = placebo; PR = peginterferon and ribavirin combined therapy; SIM = simeprevir; vs. = versus; WPAI = Work Productivity and Activity Impairment.
Note: Results of WPAI productivity score ranges from 0 to 100, with higher scores indicating more impairment in work and/or daily activities. A WPAI productivity score is available for all patients who completed the questionnaire. For patients who were not employed during the study, the score is based only on individual question 6 (multiplied by 10). The AUC_{60} for WPAI over time from baseline to week 60 was derived from a piecewise-linear model, allowing the slopes to change at weeks 4, 12, 24, 36, and 48.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

To review the validity of SVR12 as a surrogate for SVR24.

Background/findings

SVR24 is the standard primary end point for assessing the response to agents that treat CHC.[31] However, SVR12 is an emerging outcome of interest, potentially providing a means for determining treatment response earlier in either RCTs or in clinical practice. 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.[31] The authors reviewed data submitted to the FDA (2002–2011) from 15 phase 2 and phase 3 studies that included various treatment durations of pegylated interferon alfa-2a, pegylated interferon alfa-2b, albinterferon alfa-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 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.[32] This study included 781 patients with CHC, all of whom had received peginterferon/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.

Summary

A 2013 review of CHC published by authors from the FDA included 15 phase 2 and phase 3 studies (N = 13,599 patients), the majority of 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 SVR.

APPENDIX 6: SUMMARY OF CRICITAL APPRAISAL OF THE NETWORK META-ANALYSIS

1. Objective

The manufacturer conducted a network meta-analysis (NMA)[21] based on a systematic review to compare the clinical efficacy and safety of simeprevir with boceprevir and telaprevir-based triple therapies in treatment-naive and treatment-experienced patients infected with chronic hepatitis C (CHC) genotype 1. 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 randomized controlled trial (RCT) evidence directly comparing the available direct-acting antiviral (DAA) agents (in combination with pegylated interferon plus ribavirin [PR]), the manufacturer conducted a network meta-analysis (NMA) to estimate the comparative efficacy and safety of simeprevir with boceprevir and telaprevir based on the following outcomes: sustained virologic response (SVR), treatment discontinuation, withdrawals due to adverse event (WDAEs), anemia, rash, pruritus, and neutropenia. Separate NMAs were conducted for treatment-naive and treatment-experienced populations.

Methods

Eligibility Criteria

Inclusion criteria for the systematic review consisted of the following: RCTs in adult treatment-naive and relapsed or refractory genotype-1 CHC patients comparing any of the DAAs (simeprevir, boceprevir, or telaprevir) plus PR against each other or against PR alone. Trials enrolling patients coinfected with HIV, hepatitis B, non-genotype-1 hepatitis C, or acute hepatitis C were excluded.

Network Meta-analysis

Bayesian NMA models were used to analyze the outcomes of interest. Different doses of DAAs and/or durations of the triple-therapy regimens were not combined into single treatment nodes, but were kept separate. However, different regimens of dual PR therapy (peginterferon alfa-2a plus ribavirin [PaR] and peginterferon alfa-2b plus ribavirin ([PbR]), were considered to have similar efficacy and safety; hence, they were combined into a single treatment node. SVR 12 and SVR 24 were considered to be equivalent; in trials where both SVR 12 and SVR 24 were measured, the most complete data were used.

All outcomes were analyzed as dichotomous, and effect sizes were reported as odds ratios (ORs). The NMA was fitted using both random and fixed-effects models. In order to assess heterogeneity, several sensitivity analyses were undertaken, such as treating PaR and PbR as two distinct comparators and including phase 3 studies only; treatment arms employing the same DAA combination but different durations of the DAA and/or PR were merged into a single node.

The deviance information criterion (DIC) was used to compare the fixed and random-effects models. However, only results from the fixed-effects model have been included in the manufacturer's report. Inconsistency between direct and indirect estimates could not be assessed because all closed loops presented in the networks were derived from the same multi-group trials.

For fixed- and random-effects NMAs, a flat, normal prior distribution with a mean of 0 and variance of 10,000 for the log OR of treatment k relative to the baseline treatment was assumed. For random-effects analysis, a uniform prior distribution with a range of 0 to 10 was used for the between-study variance. The model was assessed for convergence by examining the caterpillar, density, and Brooks–Gelman–Rubin plots of the estimated parameters. WinBUGS version 1.4 was used for the analyses.

Results

Study and Patient Characteristics

Fifteen trials were included in the analysis; one study was considered as two separate trials due to separated randomization programs. Nine trials enrolled treatment-naive patients and six trials enrolled treatment-experienced patients (previously treated with PR).

All studies were phase 2or phase 3 RCTs. Included studies evaluated the different interventions with different dosages and different treatment durations. Table 24 below presents the dosing criteria and treatment duration used in the included studies. Figure 2 and Figure 3 below present network diagrams for treatment-naive and treatment-experienced populations, respectively.

Patient baseline characteristics were generally comparable across included trials. Age, gender, ethnicity, HCV genotype 1 subtype (1a versus 1b), stage of fibrosis, and cirrhosis (METAVIR fibrosis score), baseline viral load and IL28B genotype (CC, CT, TT) were extracted. Among trials enrolling treatment-naive patients, the median age was 47.9 years (range 44 to 50 years); the median proportion of male patients was 57.8% (range 50% to 71%) and the majority of patients were Caucasian (median 86.8%, range 73% to 99%). The median proportion of patients with HCV genotype 1a was 53.0% (range 38% to 67%), and with genotype 1b was 41.5% (range 22% to 62%). The median percentage of patients with a METAVIR fibrosis score between F0 and F2 was 82.0% (range 69% to 95%), while those with F3 and F4 (cirrhosis) were 14.0% (range 3.0% to 25%) and 7.0% (range 0% to 13.1%), respectively.

Data on additional interventions and medications used (such as medication used to treat anemia) were not extracted. Also, the duration of follow-up was not reported.

TABLE 24: DOSING CRITERIA AND TREATMENT DURATION USED FOR INCLUDED STUDIES

DAA dose	SIM	TEL	BOC
	75 mg daily,[a] or 100 mg daily,[a] or 150 mg daily	750 mg three times daily	800 mg three times daily
DAA duration			
Treatment-naive	12 weeks or 24 weeks[b]	12 weeks	24 weeks, or 28 weeks,[b] or 44 weeks,[b] or 48 weeks[†]
Treatment-experienced	[redacted][b] [redacted][b]	[redacted][b]	[redacted]
PR dose			
pegIFN alfa-2a, 180 mcg/week, RVB 1,000 to 1,200 mg/day			
pegIFN alfa-2b, 1.5 mcg/kg/week, RVB 600 to 1,400 mg/day			
pegIFN alfa-2b, 1.5 mcg/kg/week, RVB 400 to 1,000 mg/day[a]			
PR duration when used in combination with DAA (total treatment duration)			
Treatment-naive	RGT 24 or 48 weeks	12 weeks,[b] or 24 weeks,[b] or 48 weeks,[b] or RGT (24 or 48 weeks)	28 weeks,[b] or 48 weeks,[b] or RGT (28 or 48 weeks)
Treatment-experienced	[redacted]	[redacted][b] [redacted]	[redacted]
PR duration when used alone (total treatment duration)			
48 weeks			

BOC = boceprevir; DAA = direct-acting antiviral; pegIFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; RVB = ribavirin; SIM = simeprevir; TEL = telaprevir.
[a] Not a Health Canada–recommended dose.
[b] Not a Health Canada–recommended duration.

FIGURE 2: NETWORK DIAGRAM OF TREATMENT-NAIVE POPULATION

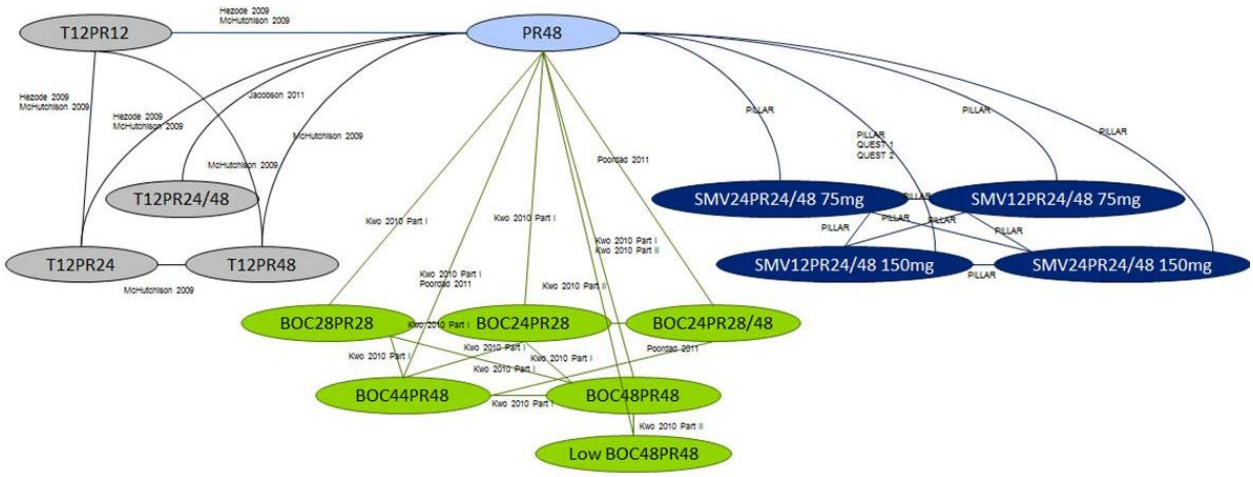

FIGURE 3: NETWORK DIAGRAM OF TREATMENT-EXPERIENCED POPULATION

Figure 3 contained confidential information and was removed at the request of the manufacturer.

Results

Sustained Virologic Response

The NMA results for SVR (12 or 24) for Health Canada–approved doses of simeprevir, telaprevir, and boceprevir triple therapy versus each other or versus PR dual therapy are presented in Table 25 below.

In both treatment-naive and treatment-experienced populations, the fixed-effect estimate of the median odds ratios (ORs) and the 95% credible interval (CrI) for triple therapy with simeprevir, telaprevir, and boceprevir were greater than 1 when compared with PR dual therapy for 48 weeks, indicating that the triple therapy with all DAAs included in this analysis resulted in significantly higher SVRs compared with PR therapy. However, when the DAA triple therapies were compared against each other, the SVR achieved with simeprevir was not significantly different than with telaprevir or boceprevir.

Two sensitivity analyses were undertaken. In the sensitivity analysis that treated PaR and PbR as two distinct comparators, results were reported only for the comparison of DAAs against PR in treatment-naive patients; similar to the base-case results, DAA triple therapies had significantly better SVRs than PR. Another sensitivity analysis, which took into account data from phase 3 trials only, revealed similar results as the primary analysis.

TABLE 25: RESULTS FROM THE NETWORK META-ANALYSES FOR SVR (12 OR 24) USING FIXED EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Treatment-naive population			
Vs. PR			
TEL12PR24/48	3.80	2.79	5.23
BOC24PR28/48	2.98	2.23	4.01
SIM12PR24/48	3.76	2.80	5.09
SIM vs. TEL or BOC			
SIM12PR24/48 vs. TEL12PR24/48	0.99	0.64	1.52
SIM12PR24/48 vs. BOC24PR28/48	1.26	0.83	1.92
Treatment-experienced population			
Vs. PR			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL or BOC			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

BOC24PR28/48 = boceprevir for 24 weeks and PR used as RGT for 28 or 48 weeks; [redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; SIM12PR24/48 = simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; TEL12PR24/48 = telaprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; vs. = versus.

Overall Treatment Discontinuation

The NMA results for overall treatment discontinuation for Health Canada–approved doses of simeprevir, telaprevir, and boceprevir triple therapy versus each other or versus PR dual therapy are presented in Table 26 below.

In the treatment-naive population, the fixed-effect estimate of the median OR and the 95% CrI for response-guided triple therapy with simeprevir and telaprevir were less than 1 when compared with PR dual therapy for 48 weeks, indicating that the triple therapy with simeprevir or telaprevir resulted in significantly reduced overall treatment discontinuation compared with PR dual therapy. When the DAA triple therapies were compared against each other, SIM12PR24/48 was associated with significantly lower treatment discontinuation when compared with TEL12PR24/48. No Health Canada–approved regimen of boceprevir triple therapy was used in the analysis; hence, no results are reported in this report.

In the treatment-experienced population, [redacted].

No sensitivity analyses were performed for this outcome.

TABLE 26: RESULTS FROM THE NETWORK META-ANALYSES FOR OVERALL TREATMENT DISCONTINUATION USING FIXED EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Treatment-naive population			
Vs. PR			
TEL12PR24/48	0.45	0.33	0.61
SIM12PR24/48	0.21	0.15	0.29
SIM vs. TEL			
SIM12PR24/48 vs. TEL12PR24/48	0.46	0.29	0.73
Treatment-experienced population			
Vs. PR			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL or BOC			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; SIM12PR24/48 = simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; TEL12PR24/48 = telaprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; vs. = versus.

Treatment Discontinuation Due to Adverse Events

The NMA results for overall treatment discontinuation due to AEs for Health Canada–approved doses of simeprevir, telaprevir, and boceprevir triple therapy versus each other or versus PR dual therapy are presented in Table 27 below.

In the treatment-naive population, the fixed-effect estimate of the median OR and the 95% CrI for response-guided triple therapy with simeprevir were less than 1 when compared with PR dual therapy for 48 weeks, indicating that the triple therapy with simeprevir significantly reduced treatment discontinuation due to AEs compared with PR dual therapy; on the other hand, there was no significant difference between telaprevir triple therapy and PR dual therapy, or between boceprevir triple therapy and PR dual therapy. When the DAA triple therapies were compared against each other, simeprevir triple therapy was associated with significantly lower treatment discontinuation due to AEs when compared with telaprevir triple therapy, while no significant difference was found between simeprevir triple therapy and boceprevir triple therapy.

In the treatment-experienced population, [redacted].

No sensitivity analyses were performed for this outcome.

TABLE 27: RESULTS FROM THE NETWORK META-ANALYSES FOR OVERALL TREATMENT DISCONTINUATION DUE TO ADVERSE EVENTS USING FIXED EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Treatment-naive population			
Vs. PR			
TEL12PR24/48	1.43	0.84	2.45
BOC24PR28/48	0.75	0.49	1.13
SIM12PR24/48	0.38	0.2	0.71
SIM vs. TEL or BOC			
SIM12PR24/48 vs. TEL12PR24/48	0.27	0.12	0.6
SIM12PR24/48 vs. BOC24PR28/48	0.51	0.24	1.07
Treatment-experienced population			
Vs. PR			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL or BOC			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

BOC24PR28/48 = boceprevir for 24 weeks and PR used as RGT for 28 or 48 weeks [redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; SIM12PR24/48 = simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; TEL12PR24/48 = telaprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; vs. = versus.

Anemia

The NMA results for anemia for Health Canada–approved doses of simeprevir, telaprevir, and boceprevir triple therapy versus each other or versus PR dual therapy are presented in Table 28 below.

In the treatment-naive population, when compared with PR dual therapy, the fixed-effect estimate of the median OR and the 95% CrI indicated that the incidence of treatment-emergent anemia was significantly higher among patients receiving boceprevir triple therapy and telaprevir triple therapy. No significant difference in anemia incidence was found between simeprevir triple therapy and PR dual therapy. Comparisons between simeprevir and the other DAAs included in this analysis show a significantly lower frequency of anemia with simeprevir triple therapy compared with boceprevir triple therapy and telaprevir triple therapy.

In treatment-experienced population, [redacted].

No sensitivity analyses were performed for this outcome.

TABLE 28: RESULTS FROM THE NETWORK META-ANALYSES FOR ANEMIA USING FIXED EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Treatment-naive population			
Vs. PR			
TEL12PR24/48	2.47	1.76	3.46
BOC24PR28/48	2.38	1.77	3.20
SIM12PR24/48	0.79	0.57	1.11
SIM vs. TEL or BOC			
SIM12PR24/48 vs. TEL12PR24/48	0.32	0.20	0.52
SIM12PR24/48 vs. BOC24PR28/48	0.33	0.21	0.52
Treatment-experienced population			
Vs. PR			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL or BOC			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

BOC24PR28/48 = boceprevir for 24 weeks and PR used as RGT for 28 or 48 weeks; [redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; SIM12PR24/48 = simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; TEL12PR24/48 = telaprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; vs. = versus.

Rash

The NMA results for rash for Health Canada–approved doses of simeprevir triple therapy, telaprevir triple therapy, and boceprevir triple therapy versus each other or versus PR dual therapy are presented in Table 29 below.

In the treatment-naive population, when compared with PR dual therapy, the fixed-effect estimate of the median OR and the 95% CrI indicated that incidence of rash was significantly higher among patients treated with telaprevir triple therapy. No significant difference in the incidence of treatment-emergent rash was found between simeprevir triple therapy and PR dual therapy or between boceprevir triple therapy and PR dual therapy. No significant differences in occurrence of rash were observed between simeprevir triple therapy and either boceprevir or telaprevir triple therapies.

In the treatment-experienced population, [redacted].

No sensitivity analyses were performed for this outcome.

TABLE 29: RESULTS FROM THE NETWORK META-ANALYSES FOR RASH USING FIXED EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Treatment-naive population			
Vs. PR			
TEL12PR24/48	1.80	1.30	2.49
BOC24PR28/48	1.14	0.81	1.61
SIM12PR24/48	1.15	0.82	1.62
SIM vs. TEL or BOC			
SIM12PR24/48 vs. TEL12PR24/48	0.64	0.4	1.02
SIM12PR24/48 vs. BOC24PR28/48	1.01	0.62	1.65
Treatment-experienced population			
Vs. PR			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL or BOC			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

BOC24PR28/48 = boceprevir for 24 weeks and PR used as RGT for 28 or 48 weeks; [redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; SIM12PR24/48 = simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; TEL12PR24/48 = telaprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; vs. = versus.

Pruritus

The NMA results for pruritus for Health Canada–approved doses of simeprevir triple therapy, telaprevir triple therapy, and boceprevir triple therapy versus each other or versus PR dual therapy are presented in Table 30 below.

In the treatment-naive population, similar to the results for rash, when compared with PR dual therapy the incidence of treatment-emergent pruritus was significantly higher among patients treated with telaprevir triple therapy, while no significant difference was found between simeprevir triple therapy and PR dual therapy or between boceprevir triple therapy and PR dual therapy. Comparisons between simeprevir and the other DAAs included in this analysis showed no significant differences between the simeprevir and the other triple therapy regimens.

In the treatment-experienced population, [redacted]

[redacted].

No sensitivity analyses were performed for this outcome.

TABLE 30: RESULTS FROM THE NETWORK META-ANALYSES FOR PRURITUS USING FIXED EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Treatment-naive population			
Vs. PR			
TEL12PR24/48	1.75	1.3	2.35
BOC24PR28/48	0.84	0.6	1.17
SIM12PR24/48	1.15	0.85	1.57
SIM versus TEL or BOC			
SIM12PR24/48 vs. TEL12PR24/48	0.66	0.43	1.01
SIM12PR24/48 vs. BOC24PR28/48	1.38	0.87	2.17
Treatment-experienced population			
Versus PR			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM versus TEL or BOC			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

BOC24PR28/48 = boceprevir for 24 weeks and PR used as RGT for 28 or 48 weeks; [redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; SIM12PR24/48 = simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; TEL12PR24/48 = telaprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; vs. = versus.

Neutropenia

The NMA results for neutropenia for Health Canada–approved doses of simeprevir triple therapy, telaprevir triple therapy, and boceprevir triple therapy versus each other or versus PR dual therapy are presented in Table 31 below.

In the treatment-naive population, no significant difference was reported between any of the three DAA triple-therapy regimens and PR dual therapy for the incidence of treatment-emergent neutropenia. However, the occurrence of neutropenia was significantly higher among patients treated with simeprevir triple therapy compared with telaprevir triple therapy, but no significant difference was reported between simeprevir triple therapy and boceprevir triple therapy.

In the treatment-experienced population, [redacted].

No sensitivity analyses were performed for this outcome.

TABLE 31: RESULTS FROM THE NETWORK META-ANALYSES FOR NEUTROPENIA USING FIXED EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Treatment-naive population			
Versus PR			
TEL12PR24/48	0.70	0.47	1.04
BOC24PR28/48	1.38	0.98	1.93
SIM12PR24/48	1.24	0.88	1.76
SIM versus TEL or BOC			
SIM12PR24/48 vs. TEL12PR24/48	1.77	1.04	3.01
SIM12PR24/48 vs. BOC24PR28/48	0.91	0.56	1.48
Treatment-experienced population			
Versus PR			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM versus TEL or BOC			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

BOC24PR28/48 = boceprevir for 24 weeks and PR used as RGT for 28 or 48 weeks; [redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; SIM12PR24/48 = simeprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; TEL12PR24/48 = telaprevir for 12 weeks and PR used as RGT for 24 or 48 weeks; [redacted]; vs. = versus.

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.[33] Details and commentary for each of the relevant items identified by ISPOR are provided in Table 32.

Strengths

The NMA appears to satisfy many of the ISPOR criteria. It was based on a systematic search to identify all relevant studies, and patient characteristics in the individual studies were well reported and appeared to be reasonably similar across the included studies. The analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian NMA models created with WinBUGS 1.4). The outcome measures assessed in the NMA were clinically relevant. A number of sensitivity analyses were performed to verify the robustness of the base-case models.

Limitations

The literature search was undertaken on December 3, 2012, which is more than one year old, and there may have been studies published since that date. Treatment regiments 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 treatment-experienced population, patients with prior relapse, prior partial response, and prior null response were all analyzed together, so it was not possible to judge if any of the medication regimens would be better in any of these subpopulations. Based on a request from the CADTH Common Drug Review (CDR), the manufacturer provided NMA results for treatment-experienced patients subgrouped into prior relapsers, prior partial responders, and prior null responders (See APPENDIX 7: ADDITIONAL INFORMATION RECEIVED FROM THE MANUFACTURER RELATED TO THE SUBMITTED NETWORK META-ANALYSIS). Studies that included only Japanese patients were excluded from the analyses; such studies should have been included in the sensitivity analysis. In addition, studies that did not include a PR treatment group, but that included two doses of one of the DAAs, were excluded as well; such studies should have been included in the analyses in order to strengthen the NMA and to assess consistency.

There was a lack of reporting of study characteristics that may have affected the findings, such as differences in inclusion/exclusion criteria and patient management (e.g., how anemia was managed), so it was not possible to assess if conducting this NMA was suitable. In addition, there was a lack of assessment of between-trial differences in outcome definition and the time period over which AEs were captured or the severity of these AEs (such as anemia). It is mentioned in the report that the risk of bias in the included studies was assessed based on the methods described in the Cochrane Handbook;[34] however, nothing was reported. Hence, it was not possible to assess whether the results of the NMA were biased by the inclusion of studies having internal validity issues. Heterogeneity is a significant concern for the evaluation of the validity of findings based on this NMA, although some sensitivity analyses were performed. For example, peginterferon alfa-2a plus ribavirin and peginterferon 2b plus ribavirin were assumed to have similar efficacy/safety profiles in this NMA. Subgroup analysis may have resulted in a breakdown of randomization, which could have comprised the validity of those sensitivity analysis results. The possibility of differences in treatment effects due to heterogeneity alone cannot be completely excluded. While sensitivity analyses were performed to test the effects of some trial-level differences on SVR outcome, they were conducted only for some outcomes.

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. Many of the results on AEs need to be interpreted with caution when no significant difference is mentioned, because with such a small number of trials it is easy to end up with results with a wide CrI that may only mean a lack of precision. The manufacturer stated that both fixed-effect and random-effect models were estimated and compared for model fit based on the DIC. However, DIC and residual deviances were only reported for SVR and anemia, not for the models of other outcomes of interest. In all cases, only results from the fixed-effect model were reported. The random-effect model may have provided different results, as results would be expected to have wider CrI that might result in different conclusions. No comparison between NMA and pair-wise meta-analysis was undertaken in order to check for consistency. Reported differences between the DAA triple-therapy regimens in treatment-experienced patients could be due to different subgroups within the patient population. For example, TEL12PR48 is recommended in prior partial and prior null responders, whereas SIM12PR24 is recommended in relapsed patients; hence,

comparison between these two regimens may not be appropriate. Finally, given that some patients would have received treatment for a shorter duration than other patients in the same RGT treatment arms, the interpretation of the AE data are complicated by differing treatment durations.

The manufacturer stated that thrombocytopenia would be assessed in the NMA; however, no results were mentioned for this AE. In addition, other AEs of interest such as gastrointestinal infection, fatigue, depression, sleep loss, and photosensitivity were not assessed. Raw data used in order to run the NMA (such as SVR and AEs) were not reported, which prohibited the validation of the data used in this analysis.

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

4. Summary

Without head-to-head trial data for simeprevir versus other DAAs, the manufacturer conducted a Bayesian NMA based on a systematic review of RCTs to compare simeprevir with telaprevir and boceprevir. Overall, the systematic review and NMA reported that triple therapy with any of the three DAAs (simeprevir, telaprevir, and boceprevir) were more effective than PR dual therapy in terms of SVR, but with more AEs (anemia, rash for telaprevir and boceprevir, pruritus for telaprevir, and neutropenia for boceprevir). No significant differences in efficacy between simeprevir and telaprevir or between simeprevir and boceprevir were reported. However, a number of differences between simeprevir and telaprevir, and between simeprevir and boceprevir were reported; in patients treated with simeprevir, there was less treatment discontinuation than with telaprevir, less discontinuation due to AEs than with telaprevir, and fewer patients experiencing anemia than with telaprevir or boceprevir. Although the NMA demonstrated sufficient methodological rigour on a number of criteria, there were some important limitations. These included the lack of reporting of study characteristics to determine suitability for conducting NMA, not assessing for inconsistency, reporting results of fixed-effect models only, and not reporting DIC for all of the analyses. These issues, in addition to the lack of any head-to-head studies, render uncertain the comparative efficacy and safety of simeprevir against telaprevir and boceprevir.

TABLE 32: 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 it seems appropriate. • Several databases were searched including MEDLINE, Embase, and The Cochrane Central Register of Controlled Trials. • Search strategy was well reported. • Inclusion/exclusion process and data extraction methods used were clearly reported.
3.	Are the outcome measures described?	• Outcomes assessed in the NMA were poorly defined and it was unclear if definition differed across trials, in addition it was not clear at which time period in the study these outcomes were captured and with what severity for the AEs.
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. • The manufacturer stated that both fixed and random-effects models were fitted for the NMA. The DIC that tests the goodness of fit of random and fixed-effect models was reported only for SVR and anemia. • A Bayesian approach was used but non-informative priors were chosen in order so that observed data are not driven by the prior chosen but be completely driven by the data analogously to a frequentist approach. • The models were conducted without covariate adjustment, also it was not possible to compare direct evidence with the indirect evidence due to the absence of head-to-head trials, and hence assessment and control of potential bias/inconsistency was insufficient. • ORs were used to present the findings.
5.	Are sensitivity analyses presented?	• Sensitivity analyses were performed for only one outcome (SVR), in one of the analysis peginterferon alfa-2a and peginterferon alfa-2b were treated as distinct comparators; another analysis was restricted to results from phase 3 trials only. • Another sensitivity analysis grouped together treatment arms with the same combination of regimens but different duration of protease inhibitors and/or PR; however, only model fit was reported, and no results on the median OR were reported. • No sensitivity analysis was undertaken on Health Canada–recommended dose only, or including Japanese population studies.
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 was well reported it was also presented in a PRISMA flow chart. • A table with study/ 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 not available.
7.	Does the study describe an assessment of model fit?	• DIC for only SVR and anemia were reported on the base-case analysis.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure including point estimates and 95% credible intervals.
9.	Sensitivity/scenario analyses	• Results of the sensitivity analyses were presented in the report.
10.	Does the discussion include	• A description/summary of main findings was presented in the conclusion

ISPOR Checklist Item		Details and Comments
	the following? • Description/summary of main findings • Internal validity of analysis External validity • Implications of results for target audience	section. • No discussion was made about internal validity. • No discussion was made regarding the generalizability of findings. • Other than the conclusion, no interpretation of results was made.

DIC = deviance information criterion; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NMA = network meta-analysis; OR = odds ratio; PR = pegylated interferon plus ribavirin; RCT = randomized controlled trial; SVR = sustained virologic response.

APPENDIX 7: ADDITIONAL INFORMATION RECEIVED FROM THE MANUFACTURER RELATED TO THE SUBMITTED NETWORK META-ANALYSIS

1. Objective

Based on a request from the CADTH Common Drug Review (CDR), the manufacturer provided additional information comparing the efficacy of simeprevir with boceprevir and telaprevir (as triple therapy) and of simeprevir, boceprevir, and telaprevir-based triple therapies against pegylated interferon plus ribavirin (PR) alone in patients who were prior relapsers, prior responders, or prior null responders. In addition, the impact of genotype Q80K polymorphism was assessed in chronic hepatitis C (CHC) genotype 1-infected patients.[35-37] This brief provides a summary and discussion of the findings.

2. Summary

[redacted] Table 33.

Results

Sustained Virologic Response in Patients with Prior Relapse

[redacted] Table 33 below.

[redacted]

TABLE 33: RESULTS FROM THE NETWORK META-ANALYSES FOR SVR (12 OR 24) IN PATIENTS WITH PRIOR RELAPSE USING FIXED-EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Vs. PR			
[redacted][a]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL or BOC			
[redacted][a]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; [redacted]; vs. = versus.

[a] [redacted]

Sustained Virologic Response in Patients with Prior Partial Response

[redacted] Table 34 below.

[redacted]

TABLE 34: RESULTS FROM THE NETWORK META-ANALYSES FOR SVR (12 OR 24) IN PATIENTS WITH PRIOR PARTIAL RESPONSE USING FIXED-EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Vs. PR			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL or BOC			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; [redacted]; vs. = versus.

Sustained Virologic Response in Patients with Prior Null Response

[redacted] Table 35 below.

[redacted]

TABLE 35: RESULTS FROM THE NETWORK META-ANALYSES FOR SVR (12 OR 24) IN PATIENTS WITH NULL RESPONSE USING FIXED-EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
Vs. PR			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL			
[redacted]	[redacted]	[redacted]	[redacted]

CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; [redacted]s; vs. = versus.

Sustained Virologic Response in Patients With or Without Genotype Q80K Polymorphism

[redacted] Table 36 below.

[redacted]

[redacted]

[redacted]

[redacted]

TABLE 36: RESULTS FROM THE NETWORK META-ANALYSES FOR SVR (12 OR 24) IN PATIENTS WITH OR WITHOUT Q80K POLYMORPHISM USING FIXED-EFFECT MODEL

	Median OR	95% CrI: lower bound	95% CrI: upper bound
SIM vs. TEL or BOC in treatment-naive patients			
Patients with Q80K			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Patients without Q80K			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL or BOC in treatment-experienced patients			
Patients with Q80K			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Patients without Q80K			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SIM vs. TEL or BOC in patients with prior relapse			
Patients with Q80K			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Patients without Q80K			
[redacted][a] vs. [redacted][a]	[redacted]	[redacted]	[redacted]
[redacted][a] vs. [redacted]	[redacted]	[redacted]	[redacted]

[redacted]; CrI = credible interval; OR = odds ratio; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; [redacted]; vs. = versus.

[a] [redacted]

3. Discussion

The methods employed in the manufacturer-submitted network meta-analysis (NMA) were assessed in APPENDIX 6: SUMMARY OF CRICITAL APPRAISAL OF THE NETWORK META-ANALYSIS. The limitations previously identified by the CDR reviewer are also pertinent to these subgroup analyses.

[redacted]

[redacted]

[redacted]

4. Summary

[redacted]

APPENDIX 8: OVERVIEW OF SAFETY AND EFFICACY OF SOFOSBUVIR

Objective

To review published randomized controlled trials (RCTs) of sofosbuvir in chronic hepatitis C (CHC) genotype 1, which reflect its Health Canada–approved dosing regimen of 400 mg once daily combined with pegylated interferon plus ribavirin (PR) for 12 weeks.

Findings

One open-label RCT (ATOMIC) and a single-group study (NEUTRINO) were included in this review. Both were manufacturer-sponsored multi-centre studies, with all but one site in the United States. Patients in both studies were treatment-naive. Patients with cirrhosis were excluded from ATOMIC, while in NEUTRINO, 20% of patients with cirrhosis were included. In ATOMIC, three cohorts were compared. The first two cohorts featured sofosbuvir-PR regimens of 12 weeks (the Health Canada–approved regimen) and 24 weeks, while the third regimen was sofosbuvir-PR for 12 weeks followed by sofosbuvir monotherapy or sofosbuvir plus ribavirin for 12 weeks. All patients in NEUTRINO received the Health Canada–approved regimen of sofosbuvir-PR for 12 weeks.

TABLE 37: COMPARISON OF STUDY CHARACTERISTICS IN NEUTRINO AND ATOMIC

	NEUTRINO[38]	ATOMIC[39]
Design	Single-group 56 centres: United States	Open-label RCT 42 centres: United States, Puerto Rico
Population	Genotype 1, 4, 5, or 6 HCV treatment-naive Serum HCV RNA ≥ 50,000 IU/mL 20% of patients could have evidence of cirrhosis	Genotype 1, 4, 5, or 6 HCV treatment-naive Serum HCV RNA ≥ 50,000 IU/mL Exclude patients with cirrhosis
Intervention	Sofosbuvir 400 mg PO daily, ribavirin PO[a] + PegIFN alfa-2a 180 mcg SC once weekly for 12 weeks	A: Sofosbuvir 400 mg PO daily + PegIFN 180 mcg SC once weekly + ribavirin PO[a] × 12 weeks B: As above, × 24 weeks C: Regimen as in A, then a further 12 weeks of sofosbuvir monotherapy or sofosbuvir + ribavirin[a]
Sample	N = 327	N = 316
Primary outcome	SVR12	SVR24

IU = international units; HCV = hepatitis C virus; IFN = interferon; PegIFN = pegylated interferon; PO = orally; RCT = randomized controlled trial; RNA = ribonucleic acid; SC = subcutaneous; SVR = sustained virologic response.
[a] Ribavirin was dosed by weight: patients < 75kg received 1,000 mg daily and patients ≥ 75 kg received 1,200 mg daily.

TABLE 38: COMPARISON OF BASELINE CHARACTERISTICS IN NEUTRINO AND ATOMIC

	NEUTRINO[38]	ATOMIC [39]		
	SOF-PR 12 N = 327	SOF-PR 12 N = 52	SOF-PR 24 N = 125	SOF-PR12 SOF/SOF-RBV 12 N = 155
Mean age, years [range] (SD)	52 (19 to 70)	51 (10)	50 (11)	50 (11)
Male, n (%)	209 (64)	35 (67)	73 (58)	106 (68)
HCV subtype, n (%): 1a	225 (69)[a]	40 (77)	85 (68)	116 (75)
1b	66 (20)	12 (23)	24 (19)	39 (25)
2	0	0	0	0
3	0	0	0	0
4	28 (9)	0	11 (9)	0
5	1 (< 1)	0	0	0
6	6 (2)	0	5 (4)	0
Mean (SD) HCV RNA, $\log_{10}$ IU/mL	6.4 (0.7)	6.5 (0.7)	6.3 (0.7)	6.4 (0.8)
HCV RNA ≥ 800,000 IU/mL, n (%)	267 (82)	NR	NR	NR
IL28B genotype, n (%) CC	95 (29)	13 (25)	36 (29)	39 (25)
CT	181 (55)	33 (64)	63 (50)	88 (57)
TT	51 (16)	6 (12)	26 (21)	28 (18)
Cirrhosis, n (%)	54 (17)			
Fibrosis stage[b]–Bridging n (%)		7 (14)	17 (14)	23 (15)
–No/minimal		9 (17)	14 (11)	20 (13)
–Portal		36 (69)	93 (74)	99 (64)

CC = homozygous normal genotype; CT = heterozygous genotype; HCV = hepatitis C virus; IU = international units; NR = not reported; PR = peginterferon + ribavirin; RNA = ribonucleic acid; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir; SVR = sustained virologic response; TT = homozygous variant genotype.

[a] One patient had mixed subtype 1a/1b infection.

[b] Equivalent METAVIR fibrosis scores: No/minimal fibrosis (0, 1); portal (2), bridging (3), and cirrhosis (4).

In NEUTRINO and ATOMIC, patients were approximately 50 years of age (mean age in NEUTRINO was 52 years and mean age in ATOMIC was 50 years), and the majority were male. In NEUTRINO, virtually all patients were genotype 1a (69%) or 1b (20%), while in ATOMIC all patients in cohort A and C were genotype 1. In ATOMIC, 9% of cohort B patients were genotype 4 and 4% were genotype 6, while the remainder of the patients were genotype 1. In NEUTRINO, the protocol stipulated that 20% of patients could have cirrhosis at baseline, and 17% were cirrhotic at baseline. In ATOMIC, the majority of patients (69%) had portal fibrosis.

TABLE 39: EFFICACY AND SAFETY RESULTS FROM NEUTRINO AND ATOMIC

	NEUTRINO	ATOMIC			
	SOF-PR12 N = 327	SOF-PR12 N = 52	SOF-PR24 N = 109	SOF-PR12 SOF12/SOF-RBV12 N = 155	
SVR12, n/N (%, [95% CI])	295/327 (90)	47 (90, [79 to 97])[a]	101 (93, [86 to 97])[a]	141 (91, [85 to 95])[a]	
-subgroup: Genotype 1	89%				
SVR24 (ITT)	NA	46 (89 [77 to 96])	97 (89 [82 to 94])	135 (87 [81 to 92])	
SVR24 (PP)	NA	46/48 (96 [86 to 100])	97/99 (98 [93 to 100])	135/139 (97 [93 to 99])	
Relapse n/N (%)	28/326 (9)	2 (4)	1 (1)	4 (3)	
-Pts completing tx	25/320 (8)				
-Pts not completing tx	3/6 (50)				
WDAE, n (%)	5 (2)	3 (6)	19 (18)	7 (5)	
SAE, n (%)	4 (1)	2 (4)	6 (5)	4 (3)	
AE, n (%)	310 (95)	Authors noted that 97% to 99% of patients had an AE			
AE with difference ≥ 10% between groups, n (%)				**SOF-PR12/SOF N = 75**	**SOF-PR12/ SOF-RBV N = 75**
-fatigue	192 (59)	25 (48)	63 (50)	48 (64)	36 (48)
-headache	118 (36)	14 (27)	38 (30)	32 (43)	32 (43)
-nausea	112 (34)	-	-	-	-
-insomnia	81 (25)	-	-	-	-
-decreased appetite	58 (18)	7 (14)	17 (14)	15 (20)	19 (25)
-flu-like illness	51 (16)	-	-	-	-
-chills	54 (17)	15 (29)	25 (20)	10 (13)	18 (24)
-pyrexia	58 (18)	18 (35)	15 (12)	5 (7)	18 (24)
-pruritus	54 (17)	-	-	-	-
-neutropenia	54 (17)	12 (23)	25 (20)	8 (11)	14 (19)
-anemia	-	7 (14)	31 (25)	13 (17)	21 (28)
-rash	-	7 (14)	26 (21)	19 (25)	19 (25)
-diarrhea	-	11 (21)	23 (18)	12 (16)	7 (9)
-arthralgia	-	15 (29)	23 (18)	5 (7)	7 (9)
-dizziness	-	8 (15)	19 (15)	4 (5)	16 (21)
AEs of special interest					
↓Neutrophils – grade 3		12 (23)	22 (18)	20 (13)	
–grade 4		1 (2)	5 (4)	7 (5)	

AE = adverse event; ITT = intention-to-treat; NA = not applicable; PP = per-protocol; PR = peginterferon + ribavirin; pts = patients; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; tx = treatment; WDAE = withdrawal due to adverse event.

[a] Responses are for genotype 1.

In ATOMIC, the primary outcome was SVR24; there was no statistically significant difference in response between any of the treatment regimens, and the proportion of patients achieving SVR24 with the Health Canada–approved regimen was 89%. Similar results were seen for SVR12, with no difference between groups, and 90% of patients achieved SVR12 with the Health Canada–approved 12-week regimen. The proportion of patients experiencing relapse was 4% with the Health Canada–approved 12-week regimen, and 1% with the longer, 24-week regimen. The primary outcome of NEUTRINO was SVR12, and the proportion of patients achieving SVR12 with sofosbuvir-PR (90%) was similar to that seen in ATOMIC.

In ATOMIC, WDAE was 6% in the sofosbuvir-PR group treated at the Health Canada–approved regimen of 12 weeks versus 18% with sofosbuvir-PR treated for 24 weeks. In NEUTRINO, withdrawals due to adverse event (WDAEs) occurred in 2% of patients. In ATOMIC, the proportion of patients with SAEs was 4% with the Health Canada–approved regimen of sofosbuvir-PR for 12 weeks; this was similar to the other two cohorts. In NEUTRINO, 1% of patients had an SAE. Total AEs were not reported for each group in ATOMIC, but were reported as ranging between 97% and 99%. In NEUTRINO, 95% of patients had an AE. The most common AEs in both studies were fatigue and headache. In ATOMIC, anemia occurred in 14% of patients in the shorter sofosbuvir-PR 12-week regimen and in 25% of patients in the sofosbuvir-PR 24-week regimen. In the group that followed 12 weeks of sofosbuvir-PR with sofosbuvir monotherapy, anemia occurred in 17% of patients, while in patients following with sofosbuvir-ribavirin for another 12 weeks, the incidence of anemia was 28%.

Summary

One open-label RCT (ATOMIC) and a single-group study (NEUTRINO) evaluated sofosbuvir-PR at the Health Canada–approved 12-week regimen in patients with CHC genotype 1. ATOMIC assigned 316 primarily genotype 1 patients to either the Health Canada–approved 12-week regimen of sofosbuvir-PR, a 24-week regimen of sofosbuvir-PR, or a 12-week regimen of sofosbuvir-PR followed by 12 weeks of either sofosbuvir monotherapy or sofosbuvir-ribavirin. NEUTRINO assigned 327 primarily genotype 1 patients to the Health Canada–approved 12-week sofosbuvir-PR regimen. In ATOMIC, 89% of patients on the Health Canada–approved regimen achieved SVR24 and 90% achieved SVR12; there was no statistically significant difference in response between any of the cohorts in this study. Results for SVR12 for the 12-week sofosbuvir-PR regimen in NEUTRINO were identical to those in the ATOMIC study. In ATOMIC, the longer 24-week sofosbuvir-PR regimen had a higher rate of WDAE (18%) than the Health Canada approved 12-week regimen (6%).

APPENDIX 9: VIROLOGIC STOPPING CRITERIA IN INCLUDED STUDIES

TABLE 40: QUEST-1, QUEST-2, AND PROMISE STOPPING CRITERIA

Stop TMC435/placebo and continue with PegIFN and RBV according to Part I of the Time and Events Schedule in case of:	
Week 4	HCV RNA levels >1,000 IU/mL
Stop PegIFN and RBV and follow Part III of the Time and Events Schedule in case of:	
Week 12	<2 $\log_{10}$ IU/mL reduction of HCV RNA compared to baseline
Week 24	Confirmed detectable and HCV RNA levels ≥ 25 IU/mL
Week 36	Confirmed detectable and HCV RNA levels ≥ 25 IU/mL

HCV = hepatitis C virus; PegIFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid.
Source: Clinical Study Reports.[19,20,28]

TABLE 41: PILLAR STOPPING CRITERIA

Stopping Criteria	**Stop all study medication (TMC435/placebo, PegIFNα-2a, and RBV) in case of:**
Week 12	< 2 $\log_{10}$ IU/mL reduction of plasma HCV RNA compared to baseline
Week 24	Confirmed detectable plasma HCV RNA (≥ 25 IU/mL detectable)
Stopping Criteria	**Stop TMC435/placebo in case of:**
Viral breakthrough (Day 1 to Week 24)	• Confirmed increase in plasma HCV RNA of > 1 $\log_{10}$ IU/mL compared with the lowest recorded on-treatment value or • Confirmed plasma HCV RNA level of > 100 IU/mL if previously below lower limit of quantification (25 IU/mL) or undetectable (< 25 IU/mL undetectable)
Stopping Criteria	**Stop PegIFNα-2a and RBV in case of:**
Week 36	Confirmed detectable plasma HCV RNA (≥ 25 IU/mL detectable)

HCV = hepatitis C virus; PegIFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid.
Source: Clinical Study Report.[18]

TABLE 42: ASPIRE STOPPING CRITERIA

Stopping Criteria	**Stop all Study Medication (TMC435/Placebo, PegIFNα-2a and RBV) in Case of:**
Week 4	< 1 $\log_{10}$ IU/mL reduction in HCV RNA compared to baseline
Week 12	< 2 $\log_{10}$ IU/mL reduction in HCV RNA compared to baseline
Week 24	Confirmed detectable HCV RNA (≥ 25 IU/mL)
Week 36	Confirmed detectable HCV RNA (≥ 25 IU/mL)
Viral breakthrough (Day 1 to Week 48)	• Confirmed increase in HCV RNA of > 1 $\log_{10}$ IU/mL compared to the lowest recorded on-treatment value, or • Confirmed HCV RNA of > 100 IU/mL if previously below LLOQ (25 IU/mL) or < 25 IU/mL undetectable

HCV = hepatitis C virus; PegIFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid.
Source: Clinical Study Report.[27]

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