Common Drug Review
Clinical Review Report

July 2015

Drug	ledipasvir/sofosbuvir (Harvoni)
Indication	For the treatment of chronic hepatitis C virus (CHC) G1 infection in adults.
Listing request	As per Health Canada indication
Manufacturer	Gilead Sciences Canada, Inc.

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ABBREVIATIONS

AE	adverse effect
BOC	boceprevir
BOC + PR	boceprevir and pegylated interferon plus ribavirin
CDEC	Canadian Drug Expert Committee
CHC	chronic hepatitis C
CI	confidence interval
CLDQ	Canadian Liver Disease Questionnaire
CLF	Canadian Liver Foundation
CTAC	Canadian Treatment Action Council
DAA	direct-acting antiviral
FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
HCV	hepatitis C virus
HRQoL	health-related quality of life
LDV	ledipasvir
LDV/SOF	ledipasvir plus sofosbuvir
LLOQ	lower limit of quantification
MCID	minimal clinically important difference
NMA	network meta-analysis
QALY	quality-adjusted life-year
P2aR	pegylated interferon 2a plus ribavirin
P2aB	pegylated interferon 2b plus ribavirin
Peg-IFN	pegylated interferon
PI	protease inhibitor
PR	pegylated interferon plus ribavirin
RAV	resistance-associated variants
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse effect
SF-36	Short-Form 36-Item Health Survey
SIM	simeprevir
SIM + PR	simeprevir and pegylated interferon plus ribavirin
SOF	sofosbuvir
SOF + PR	sofosbuvir and pegylated interferon plus ribavirin
SOF + RBV	sofosbuvir plus ribavirin
SVR	sustained virologic response
TEL	telaprevir
TEL + PR	telaprevir and pegylated interferon plus ribavirin
WPAI	Work Productivity and Activity Impairment

EXECUTIVE SUMMARY

Introduction

Hepatitis C virus (HCV) is a ribonucleic acid (RNA) virus that infects approximately 242,000 Canadians, although it is believed there are a number of infected individuals who are unaware that they have HCV. In 2009, there were more than 11,000 new cases of HCV infection, mostly due to injection drug use.[1] Of those infected, approximately 25% clear infection spontaneously (range 15% to 45%) and the remainder develop chronic hepatitis C (CHC) infection.[2-4] There are six genotypes of HCV, and although treatment strategy tends to differ depending on genotype, there is no clear evidence that genotype affects disease severity. Genotype 1 (G1) infections account for most HCV infections in Canadians (55% to 65%).[5-7] Genotypes 2 and 3 (G2 and G3) are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada respectively, according to a recent review.[8]

Prior to 2011, pegylated interferon plus ribavirin (PR) was the gold standard therapy for patients with CHC infection. Approximately half of patients with G1 CHC infection could expect to achieve sustained virologic response (SVR) with a 48-week course of PR therapy. However, a major limitation of PR regimens has been poor tolerability. In recent years, greater understanding of the hepatitis C viral replication cycle has resulted in the development of direct-acting antiviral (DAAs) drugs that target several types of non-structural proteins used to support viral replication, which resulted in a further advance in SVR rates as compared with PR regimens that did not include a DAA.[9] Currently, there are four DAAs available in Canada for use in conjunction with PR for the treatment of G1 CHC infection. These include the protease inhibitors (PIs) telaprevir (TEL), boceprevir (BOC), and simeprevir (SIM), as well as sofosbuvir (SOF), which targets HCV polymerase.

Ledipasvir/sofosbuvir (LDV/SOF) marks the first regimen approved in Canada for CHC infection that does not include PR. SOF has been approved by Health Canada and previously reviewed by the Canadian Drug Expert Committee (CDEC) as combination therapy with PR. LDV is a new drug with a novel mechanism of action involving the inhibition of non-structural protein 5A (NS5A), which is an essential component of HCV replicase. This combination is provided as a single fixed-dose tablet (90 mg LDV plus 400 mg SOF) administered orally once daily for 8 to 24 weeks depending upon prior treatment experience and the presence of cirrhosis.

Indication under review
For the treatment of chronic infection with genotype 1 hepatitis C virus in adults.
Listing criteria requested by sponsor
For the treatment of chronic infection with genotype 1 hepatitis C virus in adults.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of LDV/SOF for the treatment of chronic hepatitis C virus (HCV) G1 infection in adults.

Results and Interpretation

Included Studies

Three pivotal phase 3 trials (ION-1, ION-2, and ION-3) were included in this systematic review. All trials were multi-group, open-label, randomized controlled trials (RCTs) designed to assess various durations of LDV/SOF 90 mg/400 mg with or without ribavirin (RBV) in patients with G1 CHC infection.

ION-1 (N = 870) was a four-group, open-label trial in treatment-naive patients: LDV/SOF for 12 weeks' duration, with or without RBV, and LDV/SOF for 24 weeks' duration, with or without RBV. ION-3 (N = 647) was a three-group trial that assessed LDV/SOF for eight weeks' duration, with or without RBV, and LDV/SOF for 12 weeks, in treatment-naive patients with CHC G1 infection. ION-2 (N = 441) had the same treatment groups as ION-1, but enrolled treatment-experienced patients with CHC G1 infection who had either a relapse or non-response to an interferon-based regimen (including NS3/4A PI-containing regimens). ION-1 and ION-2 both allowed up to 20% of the study population with confirmed cirrhosis, while ION-3 excluded patients with cirrhosis. In other respects, all three trials had similar inclusion and exclusion criteria. Patients with significant comorbidities or other active clinical conditions commonly seen in the HCV population, most notably hepatitis B virus (HBV) and HIV coinfection, were excluded in all trials.

The mean age across trials was low- to mid-fifties, with the majority of the population being male. Nearly all (> 90%) patients in ION-1 and ION-3 would have been eligible for an interferon-based regimen. Approximately 15% of patients in ION-1 and 20% of patients in ION-2 had cirrhosis at baseline. In ION-2, prior non-response and relapse were both well represented, as were prior interferon-based regimens that included and did not include a PI. SOF and LDV were administered as a single combination tablet at a fixed daily dose of 90 mg ledipasvir and 400 mg sofosbuvir (LDV/SOF 90 mg/400 mg). In groups that included RBV, RBV was dosed by weight, with patients < 75 kg receiving 1,000 mg daily, and patients ≥ 75kg receiving 1,200 mg daily, both divided into two oral doses.

While these were multi-group trials, the primary end point was the comparison of SVR at 12 weeks (SVR12) in each treatment group with a historical control SVR rate. These historical control rates (60% for ION-1 and ION-3 and 25% for ION-2) were calculated using response rates in TEL and BOC trials (adjusted for the anticipated proportion of patients with cirrhosis enrolled in the ION trials), and reduced by an arbitrary percentage to account for the improved safety profile and convenience of LDV/SOF. No comparisons were made between groups in the trials for the primary outcomes aside from a secondary non-inferiority analysis in ION-3. The lack of direct comparisons against existing PI-based regimens represents an important limitation of the available evidence, as it precludes reliable estimation of the relative efficacy and safety of LDV/SOF versus other regimens. Comparisons with historical control rates may be prone to bias due to imbalances in potential confounders between the ION trial groups and historical cohorts.

Efficacy

The proportions of patients achieving SVR12 ranged from 93% to 99% in all treatment groups in ION-1, -2, and -3; all results were statistically superior to historical control SVR rates. In the treatment-naive ION-1 population, where 16% of patients had cirrhosis, 99%, 97%, 98%, and 99% of patients achieved SVR12 with LDV/SOF for 12 weeks, LDV/SOF + RBV for 12 weeks, LDV/SOF for 24 weeks, and LDV/SOF + RBV for 24 weeks, respectively.

In the treatment-experienced ION-2 population with 20% of patients with cirrhosis, 94%, 96%, 99%, and 99% achieved SVR12 with LDV/SOF for 12 weeks, LDV/SOF + RBV for 12 weeks, LDV/SOF for 24 weeks, and LDV/SOF + RBV for 24 weeks, respectively. In ION-3, the treatment-naive population without cirrhosis demonstrated SVR12 rates of 94%, 93%, and 95% with LDV/SOF for eight weeks, LDV/SOF + RBV for eight weeks, and LDV/SOF for 12 weeks, respectively. In addition, LDV/SOF + RBV for eight weeks was non-inferior to LDV/SOF for 12 weeks, with a proportional difference of –2.3% (95% confidence interval [CI], –7.5% to 2.9%). LDV/SOF for eight weeks was also non-inferior (based on a predefined margin of 12%) to LDV/SOF for 12 weeks and LDV/SOF + RBV for eight weeks, with proportional differences of –1.4% (95% CI, –6.4% to 3.6%) and 0.9% (95% CI, –3.9% to 5.7%), respectively.

In subgroup analyses, SVR12 rates remained high across treatment groups in the ION trials regardless of genotype (G1a or G1b) or presence of cirrhosis. However, in the treatment-experienced ION-2 trial, patients with cirrhosis achieved SVR12 rates of 86.4% and 81.8% in the 12-week LDV/SOF and LDV/SOF + RBV groups, respectively, while 100% of patients in the 24-week groups achieved SVR12. In ION-2, patients who had previously relapsed or failed to respond to a PI-based treatment achieved high SVR12 rates, ranging from 94% to 100% across treatment groups.

Relapse rates ranged from 0% to 5% across all treatment groups. Health Canada's review of the ION-3 trial noted a higher relapse rate in the eight-week group of LDV/SOF among patients with an initial HCV RNA ≥ 6 million IU/mL compared with those who were below this threshold. This finding is reflected in the product monograph, whereby an eight-week treatment duration is recommended only for patients with HCV RNA < 6 million IU/mL.

No patients died during treatment in any of the trials. Health-related quality of life (HRQoL) was assessed in the ION trials using a number of instruments, including the Chronic Liver Disease Questionnaire for HCV (CLDQ-HCV) and the Short-Form 36-Item Health Survey (SF-36). Most measurements were not statistically significant in ION-1, although data were not reported for all patients in this trial. In ION-2 and ION-3, small, statistically significant differences within groups were found from baseline to the end of treatment for some dimensions of these instruments. These were of uncertain clinical significance, and between-group comparisons were not reported. Given the adverse effect profile of PR-based regimens, LDV/SOF may be associated with improved quality of life compared with existing treatments. However, in the absence of comparative HRQoL data for LDV/SOF with other regimens, the extent to which HRQoL is improved with LDV/SOF remains uncertain.

To provide further evidence regarding the comparative efficacy of LDV/SOF versus other regimens, the manufacturer submitted a network meta-analysis (NMA) for the outcome of SVR. The results of this analysis suggested that LDV/SOF was superior to existing treatments. Due to the lack of non-LDV/SOF comparator groups, the ION trials could not be directly linked to the network; therefore, the manufacturer had to use alternative methods for this NMA. These essentially amounted to observational study-like comparisons between the ION cohorts and treatment groups from previous trials of PR-based regimens. An additional limitation was that aggregate data, rather than patient-level data, were incorporated in the NMA, precluding adjustment for potential confounders in the comparison of the ION trials with trials of PR-based regimens. Due to these limitations, the estimates reported in the NMA require cautious interpretation.

Harms

Overall rates of adverse effects (AEs) were high among all treatment groups in the three trials regardless of RBV or duration of treatment, ranging from 67% to 90%. AEs were mostly mild to moderate in severity; AEs leading to any study drug discontinuation were observed in fewer than 4% of patients in all treatment groups. The rates of serious AEs ranged from 0% to 8% across treatment groups in the three included trials. There did not appear to be a specific duration or regimen that was clearly associated with a definitively higher rate of serious adverse effects (SAEs).

The most common AEs reported for LDV/SOF regimens included fatigue, headache, and nausea (all > 10%). When RBV was combined with LDV/SOF, the regimen was associated with higher rates of cough, pruritus, rash, insomnia, irritability, and anemia than those that did not contain RBV. These AEs are well established, common AEs of RBV. Hematologic abnormalities, while common with PR-based regimens for HCV, occurred infrequently in all three trials, with the notable exception of anemia, a common AE of RBV, that occurred in 8% to 12% of patients on RBV-containing regimens, but in almost none of the patients who did not receive RBV. AEs relating to mood are commonly reported with PR-based regimens. Reported rates of depression were less than 3% in LDV/SOF groups, and up to 5% in groups that also included RBV. Fatigue, a common AE of PR-based regimens, was reported by fewer than 25% of patients in LDV/SOF groups, and by up to 45% in groups that also included RBV. Insomnia was reported in 5% to 12% of patients on LDV/SOF, but in 12% to 22% of patients also receiving RBV. Irritability was reported in 1% to 8% of patients on LDV/SOF, and in up to 13% of patients who received RBV. Dermatologic AEs also occurred more frequently in RBV groups, with rash occurring in 8% to 14% of patients compared with 1% to 8% of patients only receiving LDV/SOF.

While characteristic AEs associated with PR-based regimens appeared to occur less frequently with LDV/SOF, the lack of direct comparative trials makes it difficult to estimate its relative safety profile versus other regimens. Unfortunately, the manufacturer's NMA was restricted to SVR rates and did not assess relative safety.

Conclusions

LDV/SOF administered for the Health Canada–approved durations was associated with high rates of SVR12 in patients with G1 CHC infection, in both treatment-naive and treatment-experienced patients. These rates were statistically significantly higher than historical control rates for DAA-containing regimens. The addition of RBV to LDV/SOF did not appear to improve SVR12 rates. LDV/SOF appeared to be better tolerated in a number of respects compared with RBV-containing regimens in the three pivotal trials. There were no direct comparative trials of LDV/SOF against existing DAA-containing regimens. The manufacturer-submitted NMA showed higher SVR rates with LDV/SOF than with PR-based DAA regimens; however, significant methodological limitations were noted that reduce confidence in the reported effect estimates. This renders it difficult to estimate the incremental benefit on SVR of LDV/SOF compared with other regimens. HRQoL scales demonstrated mixed and marginal changes from baseline to end of therapy. Relapse rates were low throughout all the trials, although the trials have limited long-term follow-up. Although some of the characteristic AEs associated with PR appeared to occur less frequently among patients treated with LDV/SOF, the lack of comparative data against existing regimens for CHC infection makes it difficult to judge the relative safety profile of LDV/SOF.

TABLE 1: SUMMARY OF RESULTS

	ION 1 Treatment-Naive G1				ION 3 Treatment-Naive G1			ION 2 Treatment-Experienced G1			
	LDV/ SOF12 (N = 214)	**LDV/ SOF + RBV12 (N = 217)**	**LDV/ SOF24 (N = 217)**	**LDV/ SOF + RBV24 (N = 217)**	**LDV/ SOF8 (N = 215)**	**LDV/ SOF + RBV8 (N = 216)**	**LDV/ SOF12 (N = 216)**	**LDV/ SOF12 (N = 109)**	**LDV/ SOF + RBV12 (N = 111)**	**LDV/ SOF24 (N = 110)**	**LDV/SOF + RBV24 (N = 111)**
SVR12, n (%)	211 (99%)	211 (97%)	212 (98%)	215 (99%)	202 (94%)	201 (93.1%)	206 (95.4%)	102 (93.6%)	107 (96.4%)	108 (99.1%)	110 (99.1%)
95% CI	96% to 100%	94% to 99%	95% to 99%	97% to 100%	90% to 97%	89% to 96%	92% to 98%	87% to 97%	91% to 99%	95% to 100%	95% to 100%
Absolute difference between observed SVR12 and historical control[a]	39%	37%	38%	99%	34%	33.1%	35.4%	68.6%	71.4%	74.1%	74.1%
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Relapse, n/N (%)	1/213 (0.5%)	0/217	1/NR (0.5%)	0/NR	11/NR (5.1%)	9/NR (4.2%)	3/NR (1.4%)	7/108 (6.5%)	4/111 (3.6%)	0/109	0/110
Any AE	168 (78.5%)	184 (84.8%)	177 (81.6%)	200 (92.2%)	145 (67.4%)	165 (76.4%)	149 (69.0%)	73 (67.0%)	96 (86.5%)	88 (80.7%)	100 (90.1%)
SAE	1 (0.5%)	7 (3.2%)	18 (8.3%)	6 (2.8%)	4 (1.9%)	1 (0.5%)	5 (2.3%)	0	0	6 (5.5%)	3 (2.7%)
AE leading to discontinuation of any study drug	0	1 (0.5%)	4 (1.8%)	8 (3.7%)	0	2 (0.9)	2 (0.9%)	0	0	0	0

AE = adverse effect; CI = confidence interval; LDV/SOF8 = ledipasvir/sofosbuvir x 8 weeks; LDV/SOF12 = ledipasvir/sofosbuvir x 12 weeks; LDV/SOF24 = ledipasvir/sofosbuvir x 24 weeks; LDV/SOF + RBV8 = ledipasvir/sofosbuvir plus ribavirin x 8 weeks; LDV/SOF + RBV12 = ledipasvir/sofosbuvir plus ribavirin x 12 weeks; LDV/SOF + RBV24 = ledipasvir/sofosbuvir plus ribavirin x 24 weeks; NR = not reported; SAE = serious adverse effect; SVR12 = sustained virologic response at 12 weeks.

[a] Historical control rates were 60% for ION-1 and ION-3, and 25% for ION-2.

Source: Clinical Study Reports for ION-1, -2, and -3.[10-12]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hepatitis C virus (HCV) infection is caused by an enveloped, single-stranded linear ribonucleic (RNA) virus of the Flaviviridae family. It is estimated that 0.8% of Canadians (about 242,000) have chronic hepatitis C (CHC) infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[13] In 2009, 11,357 cases of HCV were reported in Canada, mostly due to injection drug use.[1] It most commonly affects people older than 30 years, and disproportionately men, although the gender gap is narrowing.[1] Other populations at higher risk for HCV infection include federal inmates, men who have sex with men, street-involved youth, and Aboriginal peoples.[1] 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 (G1) infections are the least treatment responsive, and account for most HCV infections in Canada (55% to 65%).[5-7] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, according to a recent review.[8]

Of those infected, approximately 25% clear infection spontaneously (range 15% to 45%) and the remainder develop chronic CHC infection.[2-4] Of those with CHC infection, 15% to 25% will develop progressive liver disease, end-stage liver disease, or hepatocellular carcinoma, or will require liver transplant.[14,15] Male gender, alcohol use, HIV coinfection, obesity, and increasing age are associated with an increased risk of liver disease progression. HIV coinfection is reported in 17% of patients with HCV infection in Canada.[16] While incident cases of HCV in North America and Canada[17,18] continue to decline, it is expected that liver-related morbidity and mortality will continue to increase over the coming decades, as those who are already infected age.[13,15]

1.2 Standards of Therapy

The treatment paradigm for CHC infection continues to evolve rapidly. Prior to 2011, pegylated interferon plus ribavirin (PR) was the gold standard therapy for patients with CHC infection. Approximately half of patients infected with G1 HCV, the most prevalent type of CHC infection in Canada, could expect to achieve sustained virologic response (SVR) with a 48-week course PR therapy. However, a major limitation of existing treatment regimens has been the tolerability of those that include PR. In recent years, greater understanding of the hepatitis C viral replication cycle has resulted in the development of direct-acting antiviral (DAA) drugs that target several types of non-structural proteins used to support viral replication. These regimens resulted in a further advance in SVR rates as compared with PR regimens that did not include a DAA.[9] Currently, there are four DAAs available in Canada for use in conjunction with PR for the treatment of G1 CHC infection. These include the protease inhibitors (PIs) telaprevir (TEL), boceprevir (BOC), and simeprevir (SIM), as well as sofosbuvir (SOF), which targets HCV polymerase.

1.3 Drug

Ledipasvir/sofosbuvir (LDV/SOF) marks the first regimen approved in Canada for CHC infection that does not include PR. SOF has been approved by Health Canada and previously reviewed by the CADTH Common Drug Review (CDR) as combination therapy with PR.[19] LDV is a new drug with a novel mechanism of action involving the inhibition of non-structural protein 5A (NS5A), which is an essential component of HCV replicase. The LDV/SOF combination is provided as a single fixed-dose tablet of 90 mg ledipasvir and 400 mg sofosbuvir (LDV/SOF 90 mg/400 mg) administered orally once daily for eight to 24 weeks depending upon prior treatment experience and the presence of cirrhosis.

Indication under review
For the treatment of chronic infection with genotype 1 hepatitis C virus in adults.
Listing criteria requested by sponsor
For the treatment of chronic infection with genotype 1 hepatitis C virus in adults.

TABLE 2: KEY CHARACTERISTICS OF SIMEPREVIR, BOCEPREVIR, TELAPREVIR, SOFOSBUVIR, AND LEDIPASVIR

	Simeprevir	Boceprevir	Telaprevir	Sofosbuvir	Ledipasvir
Mechanism of Action	DAA against the HCV that is a specific inhibitor of the HCV NS3·4A protease through a non-covalent, induced-fit binding into the active site of the NS3 protease.	DAA against the HCV that is a specific inhibitor of the HCV NS3/4A protease, covalently, yet reversibly binds to the NS3/4A protease active site serine (Ser139) through an (alpha)-ketoamide functional group to inhibit viral replication in HCV-infected host cells.	DAA against the HCV that is a specific inhibitor of the HCV NS3·4A protease, which is essential for viral replication.	DAA against the HCV that is mediated by a membrane-associated multi-protein replication complex. The HCV polymerase (NS5B protein) is an RNA-dependent RNA polymerase and is the essential initiating and catalytic sub-unit of this replication complex. It is critical for the viral replication cycle.	DAA against the HCV through inhibition of NS5A. No known enzymatic function has been associated with the NS5A protein; however, it is an essential component of HCV replicase.
Indication[a]	Treatment of CHC G1 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.	Treatment of CHC G1 infection, in combination with PR, 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 G1 infection, in combination with PR, 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 G1 CHC infection in adults in combination with ledipasvir. Treatment of genotypes 1 and 4 CHC infection in combination with PR, and treatment of genotypes 2 and 3 CHC infection in combination with ribavirin.	Treatment of G1 CHC infection in adults in combination with sofosbuvir.

	Simeprevir	Boceprevir	Telaprevir	Sofosbuvir	Ledipasvir
Route of Administration	Oral				
Recommended Dose	150 mg capsule once daily with PR **Treatment-naive:** Triple therapy for 12 weeks, followed by PR for additional 12 or 36 weeks based on RGT. **Treatment-experienced:** Triple therapy for 12 weeks, plus PR 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 therapy for 4 weeks, triple therapy for 24 weeks, PR therapy for a possible additional 20 weeks based on RGT. **Treatment-experienced:** PR therapy for 4 weeks, and either triple therapy for 32 weeks or triple therapy for 32 weeks plus PR 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 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: T**riple therapy for 12 weeks, PR therapy for additional 12 or 36 weeks based on RGT. **Treatment-experienced:** Triple therapy for 12 weeks, PR for additional 12 or 36 weeks based on RGT (prior-relapsers) or triple therapy for 12 weeks, PR for additional 36 weeks (prior partial and null responders). **Cirrhotic patients:** Triple therapy for 12 weeks, PR for additional 36 weeks.	**G1:** 400 mg fixed-dose combination tablet with 90 mg ledipasvir once daily for 12 weeks (24 weeks for treatment-experienced patients with cirrhosis; 8 weeks can be considered for treatment-naive patients with HCV RNA < 6 million IU/mL) **Genotypes 1 and 4:** 400 mg tablet, once daily with PR for 12 weeks. **Genotype 2:** 400 mg tablet once daily in combination with RBV for 12 weeks. **Genotype 3:** 400 mg tablet once daily in combination with RBV for 16 weeks. Consideration should be given to extending the duration of therapy beyond 16 weeks and up to 24 weeks, guided by an assessment of the potential benefits and risks for the individual patient (these factors may include cirrhosis status and treatment history).	**G1:** 90 mg fixed-dose combination tablet with 400 mg sofosbuvir once daily for 12 weeks (24 weeks for treatment-experienced patients with cirrhosis; 8 weeks can be considered for treatment-naive patients with HCV RNA < 6 million IU/mL)

	Simeprevir	Boceprevir	Telaprevir	Sofosbuvir	Ledipasvir
Serious Side Effects/ Safety Issues	Rash, pruritis, nausea	Fatigue, anemia, nausea, headache, dysgeusia	Rash, pruritus, anemia, nausea, diarrhea, hemorrhoids, anorectal discomfort, dysgeusia, fatigue, vomiting	Fatigue, headache	As combination with sofosbuvir: fatigue, headache

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral; G1 = genotype 1; HCV = hepatitis C virus; NS = non-structural protein; Peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RGT = response-guided therapy; RNA = ribonucleic acid.
[a] Health Canada indication.

2. OBJECTIVE AND METHODS

2.1 Objective

To perform a systematic review of the beneficial and harmful effects of LDV/SOF for the treatment of CHC G1 infection in adults.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with CHC G1 infection Subpopulations: • Treatment history (treatment-naive, prior relapse, prior partial response, null response) with PR or DAA plus PR therapy • Fibrosis level • HIV coinfection • Genotype subtype • Renal insufficiency • Post-liver transplant • Decompensated liver disease
Intervention	Ledipasvir/sofosbuvir 90 mg/400 mg orally once daily
Comparators	• Ledipasvir/sofosbuvir 90 mg/400 mg orally once daily in combination with ribavirin or for a different treatment duration • Placebo in combination with PR • Boceprevir in combination with PR • Telaprevir in combination with PR • Simeprevir in combination with PR • Sofosbuvir in combination with PR • Sofosbuvir in combination with ribavirin • Placebo/no treatment
Outcomes	**Key efficacy outcomes:** • Sustained virologic response • Relapse • HRQoL • Mortality (all-cause and liver-related) **Other efficacy outcomes:** • Hepatic-related morbidity outcomes (e.g., histological changes, hepatocellular carcinoma, liver failure, liver transplant) **Harms outcomes:** • SAE, WDAE, AE • Harms of special interest (rash, fatigue, anemia, neutropenia, pruritus, depression, sleep loss, nausea, photosensitivity)
Study Design	Published and unpublished RCTs

AE = adverse effects; CHC = chronic hepatitis C; DAA = direct-acting antiviral; G1 = genotype 1; HRQoL = health-related quality of life; PR = pegylated interferon plus ribavirin; RCT = randomized controlled trial; SAE = serious adverse effect; WDAE = withdrawal due to adverse effect.

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 via Ovid; Embase (1974–) via 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 concept was Harvoni (ledipasvir/ sofosbuvir).

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 October 20, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on April 15, 2015. 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, Databases (free), Internet Search. 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 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of three 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

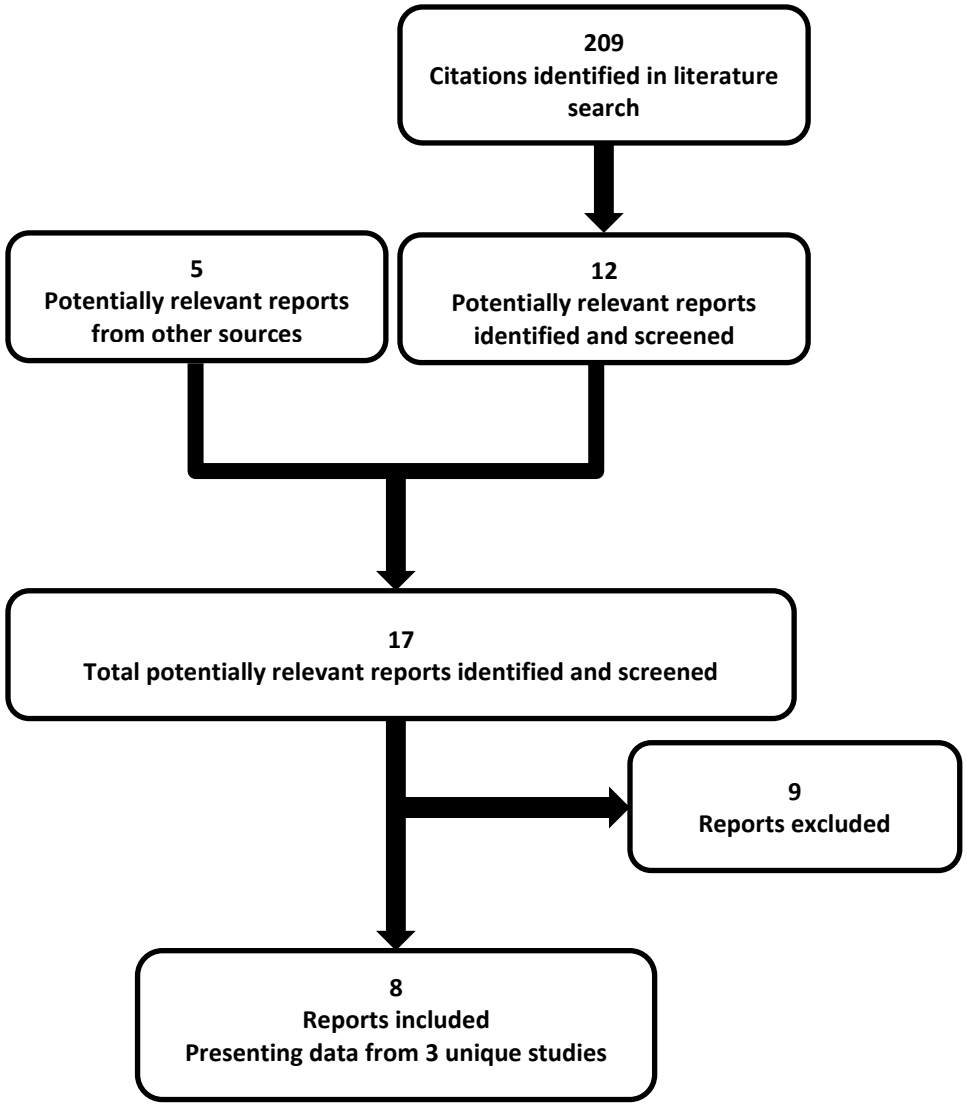


TABLE 4: DETAILS OF INCLUDED STUDIES

		ION-1 (Study 0102)	ION-3 (Study 0108)	ION-2 (Study 0109)
DESIGNS & POPULATIONS	**Study Design**	OL RCT, multi-centre	OL RCT, multi-centre	OL RCT, multi-centre
	Phase	3	3	3
	Locations	United States, Germany, France, United Kingdom, Spain, Italy	United States	United States
	Randomized (N)	870	647	441
	Inclusion Criteria	• Age ≥ 18 years • Chronic HCV[a] G1a, G1b, or G1a/1b infection with HCV RNA ≥ 10^4 IU/mL • HCV treatment-naive • Up to 20% could have had cirrhosis	• Age ≥ 18 years • Chronic HCV[a] G1a, G1b, or G1a/1b infection with HCV RNA ≥ 10^4 IU/mL • HCV treatment-naive	• Age ≥ 18 years • Chronic HCVa G1a, G1b, or G1a/1b infection with HCV RNA ≥ 104 IU/mL • Prior virologic failure with a PR regimen, including NS3/4A PI + PR regimen. Failure must not have been due to adverse effect. Failure could be defined as non-response or relapse/breakthrough • Up to 20% could have had cirrhosis
	Exclusion Criteria	• Clinical hepatic decompensation • Clinically significant illness other than HCV • Solid organ transplantation • HBV or HIV • Alcohol or drug misuse • Non-HCV liver disease • Psychiatric-related hospitalization or disability, suicide attempt	• Cirrhosis • Clinical hepatic decompensation • Clinically significant illness other than HCV • Solid organ transplantation • HBV or HIV • Alcohol or drug misuse • Non-HCV liver disease • Psychiatric-related hospitalization or disability, suicide attempt	• Clinical hepatic decompensation • Clinically significant illness other than HCV • Solid organ transplantation • HBV or HIV • Alcohol or drug misuse • Non-HCV liver disease • Psychiatric-related hospitalization or disability, suicide attempt
DRUGS	**Intervention**[b,c]	LDV/SOF x 12 weeks LDV/SOF + RBV x 12 weeks LDV/SOF x 24 weeks LDV/SOF + RBV x 24 weeks	LDV/SOF x 8 weeks LDV/SOF + RBV x 8 weeks LDV/SOF x 12 weeks	LDV/SOF x 12 weeks LDV/SOF + RBV x 12 weeks LDV/SOF x 24 weeks LDV/SOF + RBV x 24 weeks
	Comparator(s)	Historical control rate of 60%	Historical control rate of 60%	Historical control rate of 25%

		ION-1 (Study 0102)	ION-3 (Study 0108)	ION-2 (Study 0109)
DURATION	**Phase**			
	Screening	4 weeks	4 weeks	4 weeks
	Treatment	12 or 24 weeks	8 or 12 weeks	12 or 24 weeks
	Follow-up	24 weeks	24 weeks	24 weeks
OUTCOMES	**Primary End Point**	SVR12	SVR12	SVR12
	Other End Points	• SVR24 • Relapse • SF-36 • CLDQ–HCV • WPAI • FACIT • Harms	• Non-inferiority between treatment groups on SVR12 (as secondary outcome) • Virologic failure • Relapse • SF-36 • CLDQ–HCV • WPAI • FACIT • Harms	• Virologic failure • Relapse • SF-36 • CLDQ–HCV • WPAI • FACIT • Harms
NOTES	**Publications**	Afdhal 2014[20]	Kowdley 2014[21]	Afdhal 2014[22]

CLDQ–HCV = Chronic Liver Disease Questionnaire — Hepatitis C Virus; FACIT-F = Functional Assessment of Chronic Illness Therapy — Fatigue; G1a = genotype 1a; G1b = genotype 1b; G1a/1b = mixed genotype 1a/1b; HBV = hepatitis B virus; HCV = hepatitis C virus; HRQoL = health-related quality of life; LDV/SOF = ledipasvir/sofosbuvir; LDV/SOF + RBV = ledipasvir/sofosbuvir plus ribavirin; NS3 = non-structural protein 3; OL = open-label; PR = pegylated interferon; RBV = ribavirin; RCT = randomized controlled trial; RNA = ribonucleic acid; SF-36 = Short-Form (36-Item) Health Survey; SVR = sustained virologic response; SVR12/24 = sustained virologic response, 12 or 24 weeks; WPAI–Hep C = Work Productivity and Activity Impairment — Hepatitis C.

[a] Chronic HCV infection is defined as positive anti-HCV antibody test, HCV RNA, or HCV genotyping test at least six months prior to day 1 of treatment, or liver biopsy performed prior to day 1 of treatment with evidence of chronic HCV infection.

[b] LDV/SOF was dosed as a fixed oral once-daily dose of 400 mg/90 mg.

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

Sources: Clinical Study Reports for ION-1, -2, and -3;[10-12] CDR submission;[23] Health Canada reviewer's report.[24]

3.2 Included Studies

3.2.1 Description of Studies

Three pivotal phase 3 trials were included in this systematic review (ION-1, ION-2, and ION-3). ION-2 and ION-3 were multi-centre trials that took place exclusively in the United States, while ION-1 consisted of sites in both the United States and Europe. All trials were multi-group, open-label, randomized controlled trials (RCTs) designed to assess various durations of LDV/SOF 90 mg/400 mg with or without RBV in G1 CHC infection. While these were multi-group trials, their primary end points were the comparison of SVR12 in each treatment group with a historical control SVR rate. While the trials were open-label, investigators and sponsors were blinded to the final HCV RNA result.

ION-1 was a four-group, open-label trial in treatment-naive patients with CHC G1 infection. There were four groups in this trial: LDV/SOF for 12 weeks' duration, with or without RBV, and LDV/SOF for 24 weeks' duration, with or without RBV. ION-3 was a three-group trial that assessed LDV/SOF for eight weeks' duration, with or without RBV, and LDV/SOF for 12 weeks, in treatment-naive patients with CHC G1 infection. Unlike ION-1, ION-3 excluded patients with cirrhosis. ION-2 had the same treatment groups as ION-1, but enrolled treatment-experienced patients with CHC G1 infection.

Patients in all three RCTs were randomized by use of an interactive voice response system. In ION-1, randomization was stratified based on genotype subtype and presence of cirrhosis, and in ION-3, stratification was by genotype subtype alone. In ION-2, randomization was stratified by genotype subtype, presence of cirrhosis, and previous response to therapy.

Most follow-up assessments were completed at two- to four-week intervals throughout all three trials while on treatment, while post-treatment follow-up was at less frequent intervals.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

ION-1 and ION-3 were trials in the treatment-naive population, while ION-2 assessed treatment-experienced patients who had either a relapse or non-response to an interferon-based regimen (including NS3/4A PI–containing regimens). Relapse was defined as HCV RNA less than the lower limit of quantification (LLOQ) during treatment or within four weeks of treatment, but failure to achieve SVR. Non-responders were defined as those who did not achieve HCV RNA < LLOQ while on treatment. ION-1 and ION-2 both allowed up to 20% of the study population with confirmed cirrhosis, while ION-3 excluded patients with cirrhosis. In other respects, all three trials had similar inclusion and exclusion criteria. Patients with significant comorbidities commonly seen in the HCV population, most notably HBV and HIV coinfection, were excluded in all trials.

b) Baseline Characteristics

Most patient characteristics were well matched across treatment groups within each trial at baseline. All patients in all three trials were infected with HCV G1, with the exception of six patients in ION-1. The majority of patients had G1a infection. The mean age across trials was low- to mid-fifties, with the majority of the population being male. Nearly all (> 90%) patients in ION-1 and -3 would have been eligible for an interferon-based regimen. Approximately 15% of patients in ION-1 and 20% of patients in ION-2 had cirrhosis at baseline. In ION-2, prior non-response and relapse were both well represented, as were prior interferon-based regimens that included and did not include a PI. A somewhat higher proportion of patients had previously been on a regimen that included a PI in the 12-week groups of ION-2 (58% to 61% versus 46% in each of the 24-week groups).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	ION-1 Treatment-Naive G1				ION-3 Treatment-Naive G1			ION-2 Treatment-Experienced G1			
	LDV/SOF 12 (N = 214)	**LDV/SOF + RBV12 (N = 217)**	**LDV/SOF24 (N = 217)**	**LDV/SOF + RBV24 (N = 217)**	**LDV/SOF8 (N = 215)**	**LDV/SOF + RBV8 (N = 216)**	**LDV/SOF12 (N = 216)**	**LDV/SOF12 (N = 109)**	**LDV/SOF + RBV12 (N = 111)**	**LDV/SOF24 (N = 109)**	**LDV/SOF + RBV24 (N = 111)**
Age (years), mean (SD)	52 (10.7)	52 (11.5)	53 (10.3)	53 (9.9)	53 (10.2)	51 (11.7)	53 (10.6)	56 (6.9)	57 (8.0)	56 (8.3)	55 (7.8)
Male, n (%)	127 (59.3%)	128 (59.0%)	139 (64.1%)	119 (54.8%)	130 (60.5%)	117 (54.2%)	128 (59.3%)	74 (67.9%)	71 (64.0%)	74 (67.9%)	68 (61.3%)
Ethnicity, n (%)											
Caucasian	187 (87.4%)	188 (86.6%)	177 (81.6%)	183 (84.3%)	164 (76.3%)	176 (81.5%)	167 (77.3%)	84 (77.1%)	94 (84.7%)	91 (83.5%)	89 (80.2%)
Black	24 (11.2%)	26 (12.0%)	32 (14.7%)	26 (12.0%)	45 (20.9%)	36 (16.7%)	42 (19.4%)	24 (22%)	16 (14.4%)	17 (15.6%)	20 (18%)
Other	3 (1.4%)	3 (1.4%)	8 (3.7%)	8 (3.7%)	6 (2.8%)	4 (1.9%)	7 (3.2%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	2 (1.8%)
Interferon eligible, n (%)	200 (93.5%)	197 (90.8%)	198 (91.2%)	203 (93.5%)	202 (94.0%)	203 (94.0%)	201 (93.1%)	NA	NA	NA	NA
HCV genotype, n (%)											
G1a	144 (67.3%)	148 (68.2%)	146 (67.3%)	143 (65.9%)	171 (79.5%)	172 (79.6%)	172 (79.6%)	86 (78.9%)	88 (79.3%)	85 (78.0%)	88 (79.3%)
G1b	66 (30.8%)	68 (31.3%)	68 (31.3%)	71 (32.7%)	43 (20.0%)	44 (20.4%)	44 (20.4%)	23 (21.1%)	23 (20.7%)	24 (22.0%)	23 (20.7%)
G1 (unconfirmed subtype)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0	0	0	0	0
G4	1 (0.5%)	0	0	1 (0.5%)	0	0	0	0	0	0	0
Missing	2 (0.9%)	0	2 (0.9%)	1 (0.5%)	0	0	0	0	0	0	0
Baseline HCV RNA, $\log_{10}$ IU/mL, mean (SD)	6.4 (0.69)	6.4 (0.64)	6.3 (0.68)	6.3 (0.65)	6.5 (0.76)	6.4 (0.69)	6.4 (0.76)	6.5 (0.44)	6.4 (0.54)	6.4 (0.57)	6.5 (0.60)
Previous response to HCV Treatment											
Relapse/ breakthrough	NA	NA	NA	NA	NA	NA	NA	60 (55.0%)	65 (58.6%)	60 (55.0%)	60 (54.1%)
Non-responder	NA	NA	NA	NA	NA	NA	NA	49 (45.0%)	46 (41.4%)	49 (45.0%)	51 (45.9%)

	ION-1 Treatment-Naive G1				ION-3 Treatment-Naive G1			ION-2 Treatment-Experienced G1			
	LDV/SOF 12 (N = 214)	**LDV/SOF + RBV12 (N = 217)**	**LDV/SOF24 (N = 217)**	**LDV/SOF + RBV24 (N = 217)**	**LDV/SOF8 (N = 215)**	**LDV/SOF + RBV8 (N = 216)**	**LDV/SOF12 (N = 216)**	**LDV/SOF12 (N = 109)**	**LDV/SOF + RBV12 (N = 111)**	**LDV/SOF24 (N = 109)**	**LDV/SOF + RBV24 (N = 111)**
Prior HCV treatment category											
PR	NA	NA	NA	NA	NA	NA	NA	43 (39.4%)	47 (42.3%)	58 (53.2%)	59 (53.2%)
PI + PR	NA	NA	NA	NA	NA	NA	NA	66 (60.6%)	64 (57.7%)	50 (45.9%)	51 (45.9%)
IFN + RBV	NA	NA	NA	NA	NA	NA	NA	0	0	1 (0.9%)	1 (0.9%)

G1 = genotype 1; G4 = genotype 4; HCV = hepatitis C virus; LDV/SOF8 = ledipasvir/sofosbuvir x 8 weeks; LDV/SOF12 = ledipasvir/sofosbuvir x 12 weeks; LDV/SOF24 = ledipasvir/sofosbuvir x 24 weeks; LDV/SOF + RBV8 = ledipasvir/sofosbuvir plus ribavirin x 8 weeks; LDV/SOF + RBV12 = ledipasvir/sofosbuvir plus ribavirin x 12 weeks; LDV/SOF + RBV24 = ledipasvir/sofosbuvir plus ribavirin x 24 weeks; NA = not applicable; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; RNA = ribonucleic acid; SD = standard deviation.
Source: Clinical Study Reports for ION-1, -2, and -3.[10-12]

3.2.3 Interventions

LDV/SOF 90 mg/400 mg was administered as a single combination tablet once daily. Ribavirin was dosed by weight, with patients < 75 kg receiving 1,000 mg daily, and patients ≥ 75kg receiving 1,200 mg daily, both divided into two oral doses. Duration of treatment varied between treatment groups. In ION-1 and ION-2, treatment durations of LDV/SOF with or without RBV were either 12 or 24 weeks. In ION-3, two groups had eight-week durations (one of the LDV/SOF groups and the LDV/SOF + RBV group), and the other LDV/SOF group was of 12 weeks' duration. Protocols were in place for discontinuation and dose reductions for management of adverse effects (AEs). No dose reductions or restarts were permitted for LDV/SOF, but were permitted according to predefined criteria for RBV, such as the presence of anemia.

3.2.4 Outcomes

Outcome measures were consistent among all three trials. The primary efficacy outcome was the proportion of patients achieving SVR at 12 weeks (SVR12), defined as HCV RNA < LLOQ 12 weeks after stopping all study drugs. SVR12 appears to be a valid surrogate for the previous standard, SVR24, based on comparisons of SVR12 and SVR24 in trials of PR-based DAA regimens. Recent data presented at a conference from a pooled analysis of ION-1, ION-2, and ION-3 showed 100% concordance between SVR12 and SVR24 (APPENDIX 5: VALIDITY OF OUTCOME MEASURES).[25]

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

Viral resistance testing was completed at baseline for all patients using standard real-time polymerase-chain reaction technology. The HCV NS5A coding region was amplified for all patients at baseline, as well as the HCV NS5B region in a subset of patients. If virologic failure occurred, deep sequencing of NS5A and NS5B regions was completed at first virologic failure if plasma samples were available and HCV RNA was greater than 1,000 IU/mL. Blood samples were collected to determine serum levels of HCV RNA at screening and at each study visit during the treatment and post-treatment periods. The Cobas TaqMan HCV Test version 2.0, for use with the High Pure System assay, was used to quantify HCV RNA in this study. The LLOQ of the assay was 25 IU/mL.

Health-related quality of life (HRQoL) assessments were performed frequently throughout the trial and in post-treatment follow-up, but as the largest impact would be expected from the treatment phase, only end-of-treatment changes from baseline are reported in this review. HRQoL was assessed in the included trials using the Chronic Liver Disease Questionnaire (CLDQ), which is a HRQoL instrument for patients with chronic liver disease. CLDQ measures Activity/Energy, Emotion, Worry, Systemic, and CLDQ total score. All domains and total score are based on a Likert scale of 0 (worse) to 7 (best).

The trials also employed the Functional Assessment of Chronic Illness Therapy—Fatigue scale (FACIT-F), the Work Productivity and Activity Impairment (WPAI) questionnaire, and the Short-Form (36-Item) Health Survey (SF-36) to assess HRQoL.

The FACIT-F is a 40-item scale assessing fatigue and its impact on daily activities. Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale, make up the total score, ranging from 0 (worst) to 160 (best). The WPAI is an instrument used to measure the impact of a disease on work and daily activities. The work impairment domain is the sum of impairment in work productivity due to absenteeism (productivity loss due to a health-related absence from work, including personal time off, sick days off work, duration of short- or long-term disability, or worker's compensation days)

and impairment due to decreased productivity while at work (reduced performance or productivity while at work due to health reasons, including time not spent on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work. The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. It consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions (GH), and role limitations due to physical and emotional problems. Based on a panel of experts, the vitality dimension of SF-36 was considered most relevant for patients with CHC infection. Further information regarding the validity of HRQoL instruments employed in the ION trials can be found in Appendix 5: Validity of Outcome Measures. The only information regarding the minimal clinically important difference (MCID) for these outcomes was for the SF-36 vitality dimension, for which the MCID was estimated by experts at 4.2 points (range 3 to 5).

Treatment adherence was assessed at each study visit through a pill count of returned bottles. If no bottle was returned, the number of doses taken was recorded as 0.

The period of observation for collection of AEs extended from the first dose of study drug through to four weeks post-treatment.

3.2.5 Statistical Analysis

Although all three trials were multi-group trials, the primary outcome was statistically analyzed by comparing SVR12 in each group to a historical control SVR rate. In treatment-naive patients in ION-1 and ION-3, the historical control SVR12 rate was 60%, derived as follows:

- An SVR proportion of approximately 65% calculated from the telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data after adjusting for the targeted proportion of patients with cirrhosis (approximately 20%) in ION-1 and ION-3
- A 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment with LDV/SOF.

In ION-1, the planned sample size was 800 patients; 200 patients per group provided 91% power to detect a 13% improvement in SVR12 from the historical control rate of 60% using a two-sided, one-sample binomial test at a significance level of 0.0125, based on the Bonferroni correction. In ION-3, a sample size of 200 patients per group provided an anticipated power of 90% to detect a 30% difference from a 60% control rate, using a two-sided, one-sample binomial test at a significance level of 0.025, based on the Bonferroni correction. An interim analysis was completed for ION-1 after all participants reached the 12 week follow-up point after the end of study treatments. This analysis comprised the data provided by the manufacturer for this review.

In ION-3, an additional non-inferiority analysis was completed between treatment groups, using a conventional confidence interval (CI) approach and a non-inferiority margin of 12%. The trial needed 200 patients per group to achieve 90% power for this analysis.

ION-2 also compared each treatment group with a historical control rate. However, given that the population in ION-2 was treatment-experienced, a lower historical control rate of 25% was used in the statistical analysis. Because it was expected that 50% of patients in ION-2 would have been previously treated with a PI-based regimen, and the other 50% with PR alone, estimated retreatment SVR rates for these two populations were averaged to arrive at the overall control retreatment SVR rate. The average SVR rate for PR-experienced patients receiving retreatment with a PI-based regimen was estimated at

65% based on trials of boceprevir and telaprevir in treatment-experienced populations, after adjusting for the anticipated proportion of patients with cirrhosis in ION-2 (20%). The retreatment SVR rate for PI-experienced patients was estimated at 5%. This resulted in an average retreatment SVR rate across the PI- and PR-experienced populations of 35%, which was discounted by 10% to account for the ease and tolerability of treatment with LDV/SOF. The authors estimated that 100 patients were required in each treatment group to detect a 45% improvement from the historical control rate with 99% power using a two-sided, one-sample binomial test at a significance level of 0.0125, based on the Bonferroni correction.

Most secondary analyses identified in this report were based on summary statistics, as no comparisons between groups were completed. Statistical analyses for changes in HRQoL scores from baseline to end of treatment were completed using a Wilcoxon signed rank test for within-group changes.

a) Analysis Populations

In all trials, the full analysis set (FAS) and safety analysis set included all patients randomized and who received at least one dose of study drug. The primary analyses in all three trials, and the non-inferiority analysis in ION-3, were performed using the FAS.

3.3 Patient Disposition

Very few patients did not complete treatment, regardless of treatment assignment. Follow-up was mostly complete in all three pivotal trials. While overall withdrawal rates were too low to describe any definitive trends, overall withdrawals tended to be slightly higher in groups with longer treatment durations and with RBV-containing regimens.

TABLE 6: PATIENT DISPOSITION

	ION-1 Treatment-Naive G1				ION-3 Treatment-Naive G1			ION-2 Treatment-Experienced G1			
	LDV/SOF12	**LDV/SOF + RBV12**	**LDV/SOF24**	**LDV/ SOF + RBV24**	**LDV/SOF8**	**LDV/SOF + RBV8**	**LDV/SOF12**	**LDV/SOF12**	**LDV/SOF + RBV12**	**LDV/SOF24**	**LDV/SOF + RBV24**
Screened	1,015				831			551			
Enrolled	217	218	217	218	215	216	216	109	111	110	111
Enrolled and treated	214 (98.6%)	217 (99.5%)	217 (100%)	217 (99.5%)	215 (100%)	216 (100%)	216 (100%)	109 (100%)	111 (100%)	109 (99.1%)	111 (100%)
Full analysis set/ safety set	214 (98.6%)	217 (99.5%)	217 (100%)	217 (99.5%)	215 (100%)	216 (100%)	216 (100%)	109 (100%)	111 (100%)	109 (99.1%)	111 (100%)
Completed treatment	212 (99.1%)	213 (98.2%)	208 (95.9%)	205 (94.5%)	215 (100%)	213 (98.6%)	211 (97.7%)	109 (100%)	111 (100%)	107 (98.2%)	110 (99.1%)
Discontinued tx, n (%)	2 (0.9%)	4 (1.8%)	9 (4.1%)	12 (5.5%)	0	3 (1.4%)	5 (2.3%)	0	0	2 (1.8%)	1 (0.9%)
Adverse effect	0	0	4 (1.8%)	6 (2.8%)	0	1 (0.5%)	2 (0.9%)	0	0	0	0
Protocol violation	1 (0.5%)	1 (0.5%)	0	2 (0.9%)	0	0	0	0	0	2 (1.8%)	0
Withdrew consent		1 (0.5%)	3 (1.4%)	3 (1.4%)	0	0	0	0	0	0	0
Lost to follow-up	1 (.5%)	2 (0.9%)	0	1 (0.5%)	0	2 (0.9%)	2 (0.9%)	0	0	0	0
Lack of efficacy	0	0	1 (0.5%)	0	0	0	0	0	0	0	1 (0.9%)
Pregnancy	0	0	1 (0.5%)	0	0	0	0	0	0	0	0
Non-compliance	0	0	0	0	0	0	1 (0.5%)	0	0	0	0

G1 = genotype 1; LDV/SOF8 = ledipasvir/sofosbuvir x 8 weeks; LDV/SOF12 = ledipasvir/sofosbuvir x 12 weeks; LDV/SOF24 = ledipasvir/sofosbuvir x 24 weeks; LDV/SOF + RBV8 = ledipasvir/sofosbuvir plus ribavirin x 8 weeks; LDV/SOF + RBV12 = ledipasvir/sofosbuvir plus ribavirin x 12 weeks; LDV/SOF + RBV24 = ledipasvir/sofosbuvir plus ribavirin x 24 weeks.
Source: Clinical Study Reports for ION-1, -2, and -3.[10-12]

3.4 Exposure to Study Treatments

Treatment durations were consistent with assigned treatment group assignments in each of the trials. In ION-1, the mean durations of treatment were 12.1 weeks, 12.0 weeks, 23.6 weeks, and 23.7 weeks in the LDV/SOF for 12 weeks, LDV/SOF + RBV for 12 weeks, LDV/SOF for 24 weeks, and LDV/SOF + RBV for 24 weeks, respectively. In ION-3, mean durations of treatment were 8.1 weeks, 8.0 weeks, and 12.0 weeks in LDV/SOF for eight weeks, LDV/SOF + RBV for eight weeks, and LDV/SOF for 12 weeks, respectively. In ION-2, mean treatment durations were 12.2 weeks, 12.1 weeks, 23.9 weeks, and 24.0 weeks in LDV/SOF for 12 weeks, LDV/SOF + RBV for 12 weeks, LDV/SOF for 24 weeks, and LDV/SOF + RBV for 24 weeks, respectively.

3.5 Critical Appraisal

3.5.1 Internal Validity

ION-1, -2, and -3 were randomized trials comparing various treatment durations of LDV/SOF with or without RBV to historical control rates. Randomization was well described and effective, but allocation concealment procedures were not well reported. The trials were adequately powered, and follow-up was near complete in the trials.

There are some key limitations in these trials, consistent among all three. While these were all multi-group trials, the primary outcome of interest, the efficacy of LDV/SOF with or without RBV in the treatment of HCV as compared with existing treatments cannot be ascertained directly from the trial. The primary analysis of each trial compares the active treatments to a historical control. The historical control SVR rates are consistent with those used in the uncontrolled pivotal trials for SOF+IR+RBV. However, there are important limitations to using a historical control, as this approach essentially amounts to comparing one observational cohort with another. The purpose of an RCT is to ensure that confounders are evenly distributed among groups, increasing the chance that the observed difference (if any) is due to the interventions being assessed and not to another variable. In the case of a historical control, no guarantee can be made that the patient populations were truly similar aside from the intervention. Although the historical control rate was adjusted for the proportion of patients with cirrhosis, which can affect the likelihood of achieving SVR, there could be other patient factors that also affect SVR rates (e.g., adherence to treatment regimens, genotype). Furthermore, the ION trials and the trials from which the historical control rates were derived did not take place in the same time period. This opens the possibility that changes in clinical practice — for example, greater familiarity with the DAAs — may bias the observed treatment differences. Finally, the reduction in the historical control rate of 5% to 10% for the anticipated improvement of LDV/SOF in safety and convenience over existing regimens is arbitrary. No rationale was provided for this adjustment, nor is it clear why considerations of safety and convenience should be conflated with efficacy rather than considered separately. Despite the limitations of using a historical control, the FDA accepted this trial design for these new drug regimens in the treatment of CHC infection.[26] However, the draft guidance document produced by the FDA noted that future treatments should use alternate study designs with an active control once pegylated interferon (Peg-IFN)–free regimens are available.

In ION-3, no justification for a non-inferiority margin of 12% was provided. However, the study was adequately powered for this analysis. Only intention-to-treat (ITT) analysis was used in this calculation, which tends to bias toward achieving non-inferiority versus a per-protocol analysis; however, most patients completed the trial. Therefore the two populations would not be expected to differ greatly.

As all three trials were open label, all involved groups were aware of treatment assignments and outcome results, aside from post-treatment HCV RNA, which was blinded to investigators and the study sponsor until the point of interim analysis. While the lack of blinding may have minimal impact on objective outcomes such as SVR, it may be a concern for more subjective measurements, such as HRQoL measures or AEs. Knowledge of treatment assignment could have resulted in some degree of reporting bias, for example, due to expectations of more AEs with RBV, or of better tolerability with an interferon-free regimen.

3.5.2 External Validity

Overall, the three trials represent a chronic HCV population with minimal comorbidities. The generalizability of trial results may be limited for more complex patients, as important and common comorbidities, including HIV coinfection, were listed as exclusion criteria for all three trials. A relatively large percentage of patients are coinfected with HCV and HIV, and there is evidence that HIV coinfection can accelerate the progression of CHC to important complications such as cirrhosis and end-stage liver disease. Data were recently presented at two conferences for a recently completed single-group trial of 50 patients with CHC and HIV coinfection that suggest similar SVR12 rates (98%) in this population, as with the populations studied in the three pivotal trials.[27,28] However, these data have not been published and full results are not yet available. Patients with other major comorbidities and psychiatric hospitalizations were also not well represented in the trials, based on the listed exclusion criteria. Only a relatively small number of patients (up to 20%) in ION-1 and ION-2, and none in ION-3, had cirrhosis, limiting the extent of evidence in this population.

While LDV/SOF has potential advantages over regimens containing interferon in terms of tolerability for all patients with CHC infection, patients who are ineligible for interferon-based regimens particularly stand to benefit. However, more than 90% of patients in ION-1 and ION-3 were eligible for interferon treatment; hence there is limited evidence from these trials regarding the efficacy and safety of LDV/SOF in interferon-ineligible patients.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported (Section 2.2, Table 3). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Key Efficacy Outcomes

a) SVR12

The proportions of patients achieving SVR12 ranged from 93% to 99% in all treatment groups in ION-1, ION-2, and ION-3; all results were statistically superior to historical control SVR rates (Table 7). In ION-3, LDV/SOF + RBV for eight weeks was non-inferior to LDV/SOF for 12 weeks, with a proportional difference of –2.3% (95% CI, –7.5% to 2.9%). LDV/SOF for eight weeks was also non-inferior to LDV/SOF for 12 weeks and LDV/SOF + RBV for eight weeks, with proportional differences of –1.4% (95% CI, 6.4% to 3.6%) and 0.9% (95% CI, –3.9% to 5.7%), respectively.

In key subgroup analyses (by genotype and cirrhosis), SVR12 rates remained high regardless of genotype (1a or 1b) or the presence of cirrhosis (APPENDIX 4: DETAILED OUTCOME DATA). However, in the treatment-experienced ION-2 trial, patients with cirrhosis achieved SVR12 rates of 86.4% and 81.8% in the 12-week LDV/SOF and LDV/SOF + RBV groups, respectively, while 100% of patients in the 24-week groups achieved SVR12. In ION-2, patients who had previously relapsed or failed to respond to a PI-based treatment still achieved high SVR12 rates, ranging from 94% to 100% across treatment groups.

b) Relapse

In ION-1, a single patient relapsed in each of the 12-week and 24-week LDV/SOF treatment groups. Only the patient in the 12-week group tested for reduced susceptibility to LDV at both baseline and relapse. One patient in the 24-week treatment group of LDV/SOF had virologic failure during treatment, which was associated with documented non-compliance and phenotypic resistance to LDV. In ION-3, 23 patients relapsed in total, with 11, nine, and three patients in LDV/SOF for eight weeks, LDV/SOF + RBV for eight weeks, and LDV/SOF for 12 weeks, respectively. Ten of these patients had resistance-associated variants (RAVs) to LDV at baseline, of whom nine continued to express that variant at the time of relapse. Thirteen patients did not show RAVs at baseline, but at the time of relapse, six of the 13 showed RAVs. Twelve patients in ION-2 relapsed, 11 of whom were in the 12-week groups (seven in LDV/SOF and four in LDV/SOF + RBV). Five of these patients demonstrated RAV at baseline and all showed RAV at time of relapse. One case of relapse was attributed to non-adherence; this patient was in the 24-week group of LDV/SOF.

The Health Canada reviewer's report[24] noted higher relapse rates in the ION-3 LDV/SOF eight-week group among patients with an initial HCV RNA ≥ 6 million IU/mL (9.8%) compared with those who had an initial HCV RNA < 6 million IU/mL (1.6%). No such discrepancy was observed in the 12-week LDV/SOF group. This finding is reflected in the product monograph, whereby an eight-week treatment duration is recommended only for patients with HCV RNA < 6 million IU/mL.

c) Mortality

There were no deaths in ION-1 (although there was one death post-follow-up; see the Other Efficacy Outcomes section), ION-2, or ION-3.

d) Health-Related Quality of Life

HRQoL data were not reported for all patients in ION-1, but were reported for most patients in ION-2 and ION-3. Most measurements were not statistically significant in ION-1. In ION-2 and ION-3, small, statistically significant differences within groups were found from baseline to the end of treatment for the SF-36 Mental Component Score (MCS) and Physical Component Score (PCS). In ION-2, groups that included RBV had statistically significant negative changes from baseline in the SF-36 PCS (–1.2 and –3.0 for the 12- and 24-week groups, respectively) and MCS (–0.2 and –0.6 for the 12- and 24-week groups, respectively), as compared with slightly positive scores for groups that did not include RBV (PCS: 2.5 and 2.0 for the 12- and 24-week groups, respectively; MCS: 1.8 and 1.7 for the 12- and 24-week groups, respectively). In ION-3, the group with RBV failed to achieve any statistically significant difference from baseline for the SF-36 PCS score, but was negative for the MCS score (–3.4), as compared with positive scores for the 8- and 12-week groups without RBV (PCS: 1.5 and 1.8 for the eight- and 12-week groups, respectively; MCS: 2.1 and 1.2 for the eight- and 12-week groups, respectively). Similarly for the other scales (CLDQ-HCV, FACIT-F, and WPAI), not all scores achieved statistical significance between end of therapy and baseline, and for those that did, the absolute differences in scores were small and associated with large standard deviations. There were no statistical comparisons between treatment groups for measures of HRQoL.

e) Other Efficacy Outcomes

One patient had liver failure secondary to HCV infection and alcohol use that started post-treatment day 38 in ION-1. This patient died on day 121 post-treatment.

TABLE 7: KEY EFFICACY OUTCOMES

	ION-1 Treatment-Naive G1				ION-3 Treatment-Naive G1			ION-2 Treatment-Experienced G1			
	LDV/ SOF12 (N = 214)	**LDV/SOF + RBV12 (N = 217)**	**LDV/SOF24 (N = 217)**	**LDV/SOF + RBV24 (N = 217)**	**LDV/ SOF8 (N = 215)**	**LDV/SOF + RBV8 (N = 216)**	**LDV/ SOF12 (N = 216)**	**LDV/ SOF12 (N = 109)**	**LDV/SOF + RBV12 (N =111)**	**LDV/ SOF24 (N =110)**	**LDV/SOF + RBV24 (N = 111)**
SVR12											
n (%)	211 (99%)	211 (97%)	212 (98%)	215 (99%)	202 (94%)	201 (93.1%)	206 (95.4%)	102 (93.6%)	107 (96.4%)	108 (99.1%)	110 (99.1%)
95% CI	96% to 100%	94% to 99%	95% to 99%	97% to 100%	90% to 97%	89% to 96%	92% to 98%	87% to 97%	91% to 99%	95% to 100%	95% to 100%
Absolute difference between observed SVR12 and historical control[a]	39%	37%	38%	99%	34%	33.1%	35.4%	68.6%	71.4%	74.1%	74.1%
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Relapse, n/N (%)	1/213 (0.5%)	0/217	1/NR (0.5%)	0/NR	11/NR (5.1%)	9/NR (4.2%)	3/NR (1.4%)	7/108 (6.5%)	4/111 (3.6%)	0/109	0/110
Mortality, n (%)	0	0	0	0	0	0	0	0	0	0	0
HRQoL: SF-36 PCS	N = 50	N = 48	N = 51	N = 47							
Mean (SD) baseline	49.4 (9.71)	51.0 (8.06)	50.5 (8.63)	46.8 (11.12)	48.8 (10.94)	49.7 (9.35)	50.3 (9.17)	47.7 (9.73)	49.0 (9.01)	48.2 (8.94)	49.3 (9.69)
Mean (SD) change at EOT	1.7 (6.67)	–1.3 (6.21)	0.6 (7.25)	0.2 (6.58)	1.5 (5.86)	0.7 (7.42)	1.8 (6.85)	2.5 (5.45)	–0.2 (6.78)	2.0 (5.93)	–0.6 (6.72)
P value	0.10	0.21	0.18	0.99	< 0.001	0.58	< 0.001	< 0.001	0.62	0.001	0.39
HRQoL: SF-36 MCS	N = 50	N = 48	N = 51	N = 47							
Mean (SD) baseline	48.9 (11.85)	50.1 (10.59)	50.8 (10.79)	44.9 (13.11)	50.3 (10.85)	51.0 (10.13)	50.3 (10.92)	49.3 (10.98)	50.2 (10.91)	50.4 (11.09)	50.6 (10.34)
Mean (SD) change at EOT	2.0 (9.74)	–0.6 (9.63)	–0.8 (10.14)	2.4 (11.55)	2.1 (9.16)	–3.4 (10.16)	1.2 (9.40)	1.8 (6.92)	–1.2 (9.43)	1.7 (10.20)	–3.0 (10.42)
P value	0.012	0.81	0.94	0.29	< 0.001	< 0.001	0.032	0.014	0.22	0.025	0.014
CLDQ-HCV	N = 51	N = 51	N = 51	N = 49							
Mean (SD) baseline	5.2 (1.21)	5.5 (0.99)	5.4 (1.16)	5.0 (1.23)	5.4 (1.17)	5.4 (1.19)	5.4 (1.15)	5.2 (1.13)	5.4 (1.17)	5.4 (1.12)	5.5 (1.05)
Mean (SD) change at EOT	0.5 (0.83)	0.2 (0.98)	0.4 (0.89)	0.3 (1.08)	0.4 (0.76)	0.2 (0.91)	0.5 (0.91)	0.4 (0.75)	0.1 (0.97)	0.4 (0.75)	0.0 (0.82)
P value	< 0.001	0.052	< 0.001	0.028	< 0.001	0.008	< 0.001	< 0.001	0.24	< 0.001	0.87
FACIT-F Total Score	N = 50	N = 49	N = 51	N = 45							

	ION-1 Treatment-Naive G1				ION-3 Treatment-Naive G1			ION-2 Treatment-Experienced G1			
	LDV/ SOF12 (N = 214)	**LDV/SOF + RBV12 (N = 217)**	**LDV/SOF24 (N = 217)**	**LDV/SOF + RBV24 (N = 217)**	**LDV/ SOF8 (N = 215)**	**LDV/SOF + RBV8 (N = 216)**	**LDV/ SOF12 (N = 216)**	**LDV/ SOF12 (N = 109)**	**LDV/SOF + RBV12 (N =111)**	**LDV/ SOF24 (N =110)**	**LDV/SOF + RBV24 (N = 111)**
Mean (SD) baseline	121.6 (29.77)	125.1 (25.96)	121.1 (28.72)	112.1 (31.63)	124.5 (30.98)	126.2 (28.59)	125.2 (28.24)	121.3 (26.86)	123.8 (27.51)	122.8 (26.17)	123.5 (26.07)
Mean (SD) change at EOT	8.8 (19.64)	–0.5 (20.28)	7.6 (24.90)	5.1 (22.22)	6.4 (17.28)	–1.8 (24.32)	5.7 (23.10)	7.3 (14.76)	–0.9 (23.60)	8.4 (19.47)	–2.3 (23.79)
P value	0.003	0.96	0.009	0.16	< 0.001	0.55	< 0.001	< 0.001	0.46	< 0.001	0.30
WPAI-Hep C: Work	N = 34	N = 26	N = 31	N = 22	N = 121	N = 125	N = 124	N = 72	N = 68	N = 68	N = 63
Total % overall work impairment — mean (SD)	7.2 (12.35)	8.4 (17.96)	17.2 (26.71)	7.2 (19.55)	10.2 (20.11)	9.7 (18.81)	6.9 (15.88)	10.7 (18.54)	14.7 (23.26)	11.8 (21.04)	14.6 (23.26)
Mean (SD) change at EOT	–3.6 (19.52)	7.1 (19.00)	–7.3 (17.73)	0.3 (15.74)	–3.3 (17.44)	5.3 (28.06)	3.1 (19.52)	1.1 (18.14)	3.3 (24.05)	–5.0 (24.32)	3.4 (20.22)
P value	0.12	0.16	0.038	1.00	0.018	0.05	0.17	0.92	0.33	0.055	0.17
WPAI-Hep C: Activity	N = 50	N = 49	N = 50	N = 47	N = 213	N = 210	N = 210	N = 107	N = 108	N = 106	N = 109
Total % overall activity impairment — mean (SD)	13.4 (22.28)	12.9 (23.63)	17.8 (27.80)	27.7 (33.25)	17.7 (26.79)	16.6 (27.24)	15.4 (25.53)	19.5 (27.24)	15.7 (24.77)	16.9 (26.09)	19.6 (26.00)
Mean (SD) change at EOT	–7.0 (26.15)	3.9 (24.27)	–8.5 (28.66)	–5.3 (27.44)	–4.9 (22.84)	1.7 (27.05)	–4.9 (25.39)	–5.5 (17.76)	1.7 (28.56)	–7.2 (24.47)	–0.8 (26.96)
P value	0.056	0.17	0.054	0.38	<0.001	0.19	0.004	0.001	0.71	0.002	0.94

G1 – genotype 1; CI = confidence interval; CLDQ-HCV = Chronic Liver Disease Questionnaire — Hepatitis C Virus; EOT = end of treatment; FACIT-F = Functional Assessment of Chronic Illness Therapy — Fatigue; G1 = G1; HRQoL = health-related quality of life; LDV/SOF8 = ledipasvir/sofosbuvir x 8 weeks; LDV/SOF12 = ledipasvir/sofosbuvir x 12 weeks; LDV/SOF24 = ledipasvir/sofosbuvir x 24 weeks; LDV/SOF + RBV8 = ledipasvir/sofosbuvir plus ribavirin x 8 weeks; LDV/SOF + RBV12 = ledipasvir/sofosbuvir plus ribavirin x 12 weeks; LDV/SOF + RBV24 = ledipasvir/sofosbuvir plus ribavirin x 24 weeks; SD = standard deviation; SF-36 PCS/MCS = Short-Form 36 Physical Component Score or Mental Component Score; SVR12 = sustained virologic response at 12 weeks; WPAI-Hep C = Work Productivity and Activity Impairment — Hepatitis C.

[a] Historical control rates were 60% for ION-1 and ION-3, and 25% for ION-2.

Source: Clinical Study Reports for ION-1, -2, and -3.[10-12]

3.7 Harms

3.7.1 Adverse Effects

Overall rates of patients experiencing at least one AE were high among all treatment groups in the three trials regardless of RBV or duration of treatment, ranging from 67% to 90%. AEs reported were mostly mild to moderate in nature.

3.7.2 Serious Adverse Effects

The rates of serious adverse effects (SAEs) ranged from 0% to 8% across treatment groups in the three included trials. There did not appear to be a specific duration or regimen that was clearly associated with a definitively higher rate of SAEs. Interestingly, in ION-1 and ION-2, the overall rate of SAEs in the 24-week groups was higher in the RBV-free groups than in the groups containing RBV.

3.7.3 Withdrawals Due to Adverse Effects

AEs leading to any study drug discontinuation were observed in fewer than 4% of patients in all treatment groups.

3.7.4 Notable Harms

The most common AEs reported for LDV/SOF regimens included fatigue, headache, and nausea (all > 10%). When RBV was combined with LDV/SOF, the regimen was associated with higher rates of cough, pruritus, rash, insomnia, irritability, and anemia than those that did not contain RBV. These are known AEs of RBV. Hematologic abnormalities occurred infrequently in all three trials, with the notable exception of anemia, which occurred in 8% to 12% of patients on RBV-containing regimens but in almost none of the patients in groups that did not contain RBV. AEs relating to mood are commonly reported with comparator regimens in the treatment of HCV. Depression, irritability, insomnia, and fatigue were reported in all treatment groups in the three pivotal trials. Reported rates of depression were less than 3% in LDV/SOF groups, and up to 5% in groups that also included RBV. Fatigue was reported by fewer than 25% of patients in LDV/SOF groups, and by up to 45% in groups that also included RBV. Insomnia was reported in 5% to 12% of patients on LDV/SOF, but in 12% to 22% of patients also receiving RBV. Irritability was reported in 1% to 8% of patients on LDV/SOF, and in up to 13% of patients who received RBV. Dermatologic AEs also occurred more frequently in RBV groups, with rash occurring in 8% to 14% of patients receiving RBV compared with 1% to 8% of patients receiving only LDV/SOF.

TABLE 8: HARMS

	ION-1 Treatment-Naive G1				ION-3 Treatment-Naive G1			ION-2 Treatment-Experienced G1			
	LDV/ SOF12 (N = 214)	LDV/SOF + RBV12 (N = 217)	LDV/ SOF24 (N = 217)	LDV/SOF + RBV24 (N = 217)	LDV/ SOF8 (N = 215)	LDV/SOF + RBV8 (N = 216)	LDV/ SOF12 (N = 216)	LDV/ SOF12 (N = 109)	LDV/SOF + RBV12 (N = 111)	LDV/ SOF24 (N = 110)	LDV/SOF + RBV24 (N = 111)
AEs											
Any AE	168 (78.5%)	184 (84.8%)	177 (81.6%)	200 (92.2%)	145 (67.4%)	165 (76.4%)	149 (69.0%)	73 (67.0%)	96 (86.5%)	88 (80.7%)	100 (90.1%)
SAE	1 (0.5%)	7 (3.2%)	18 (8.3%)	6 (2.8%)	4 (1.9%)	1 (0.5%)	5 (2.3%)	0	0	6 (5.5%)	3 (2.7%)
AE leading to discontinuation of any study drug	0	1 (0.5%)	4 (1.8%)	8 (3.7%)	0	2 (0.9)	2 (0.9%)	0	0	0	0
AE leading to discontinuation of LDV/SOF	0	0	4 (1.8%)	6 (2.8%)	0	1 (0.5%)	2 (0.9%)	0	0	0	0
Common AEs											
Fatigue	44 (20.6%)	79 (36.4%)	53 (24.4%)	82 (37.8%)	45 (20.9%)	75 (34.7%)	49 (22.7%)	23 (21.1%)	45 (40.5%)	26 (23.9%)	50 (45.0%)
Headache	52 (24.3%)	49 (22.6%)	54 (24.9%)	64 (29.5%)	20 (14.0%)	54 (25.0%)	22 (15.3%)	28 (25.7%)	26 (23.4%)	25 (22.9%)	(35 (31.5%)
Insomnia	16 (7.5%)	45 (20.7%)	26 (12.0%)	47 (21.7%)	11 (5.1%)	26 (12.0%)	15 (6.9%)	10 (9.2%)	18 (16.2%)	4 (3.7%)	19 (17.1%)
Nausea	24 (11.2%)	37 (17.1%)	29 (13.4%)	32 (14.7%)	15 (7.0%)	38 (17.6%)	24 (11.1%)	13 (11.9%)	20 (18.0%)	7 (6.4%)	25 (22.5%)
Asthenia	14 (6.5%)	23 (10.6%)	20 (9.2%)	26 (12.0%)	1 (0.5%)	4 (1.9%)	1 (0.5%)	0	0	2 (1.8%)	3 (2.7%)
Diarrhea	24 (11.2%)	18 (8.3%)	24 (11.1%)	14 (6.5%)	15 (7.0%)	13 (6.0%)	9 (4.2%)	7 (6.4%)	5 (4.5%)	9 (8.3%)	17 (15.3%)
Rash	16 (7.5%)	21 (9.7%)	15 (6.9%)	27 (12.4%)	3 (1.4%)	19 (8.8%)	5 (2.3%)	2 (1.8%)	11 (9.9%)	6 (5.5%)	16 (14.4%)
Irritability	11 (5.1%)	17 (7.8%)	17 (7.8%)	24 (11.1%)	3 (1.4%)	29 (13.4%)	9 (4.2%)	2 (1.8%)	13 (11.7%)	4 (3.7%)	12 (10.8%)
Cough	6 (2.8%)	21 (9.7%)	16 (7.4%)	25 (11.5%)	3 (1.4%)	12 (5.6%)	7 (3.2%)	5 (4.6%)	16 (14.4%)	5 (4.6%)	16 (14.4%)
Pruritis	11 (5.1%)	22 (10.1%)	8 (3.7%)	20 (9.2%)	2 (0.9%)	16 (7.4%)	5 (2.3%)	5 (4.6%)	10 (9.0%)	2 (1.8%)	10 (9.0%)
Depression	5 (2.3%)	6 (2.8%)	5 (2.3%)	11 (5.1%)	4 (1.9%)	7 (3.2%)	4 (1.9%)	0	4 (3.6%)	3 (2.8%)	3 (2.7%)
Photosensitivity	3 (1.4%)	0	1 (0.5%)	2 (0.9%)	0	1 (0.5%)	1 (0.5%)	0	0	1 (0.9%)	2 (1.8%)
Hematologic AEs											
Anemia	0	25 (11.5%)	0	21 (9.7%)	2 (0.9%)	17 (7.9%)	2 (0.9%)	0	9 (8.1%)	1 (0.9%)	12 (10.8%)

	ION-1 Treatment-Naive G1				ION-3 Treatment-Naive G1			ION-2 Treatment-Experienced G1			
	LDV/ SOF12 (N = 214)	**LDV/SOF + RBV12 (N = 217)**	**LDV/ SOF24 (N = 217)**	**LDV/SOF + RBV24 (N = 217)**	**LDV/ SOF8 (N = 215)**	**LDV/SOF + RBV8 (N = 216)**	**LDV/ SOF12 (N = 216)**	**LDV/ SOF12 (N = 109)**	**LDV/SOF + RBV12 (N = 111)**	**LDV/ SOF24 (N = 110)**	**LDV/SOF + RBV24 (N = 111)**
Lymphocyte count < 350/mm^3	0	1 (0.5%)	0	0	0	1 (0.5%)	0	0	1 (0.9%)	0	1 (0.9%)
Neutrophil count 500 to < 750/mm^3	1 (0.5%)	0	3 (1.4%)	0	0	1 (0.5%)	1 (0.5%)	0	0	0	0
Platelet count 25,000 to < 50,000/mm^3	1 (0.5%)	0	1 (0.5%)	0	NR	NR	NR	1 (0.9%)	0	2 (1.8%)	0

AE = adverse effect; G1 = genotype 1; LDV/SOF = ledipasvir/sofosbuvir; LDV/SOF8 = ledipasvir/sofosbuvir x 8 weeks; LDV/SOF12 = ledipasvir/sofosbuvir x 12 weeks; LDV/SOF24 = ledipasvir/sofosbuvir x 24 weeks; LDV/SOF + RBV8 = ledipasvir/sofosbuvir plus ribavirin x 8 weeks; LDV/SOF + RBV12 = ledipasvir/sofosbuvir plus ribavirin x 12 weeks; LDV/SOF + RBV24 = ledipasvir/sofosbuvir plus ribavirin x 24 weeks; SAE = serious adverse effect.
Source: Clinical Study and Published Reports for ION-1, -2, and -3.[10-12,20-22]

4. DISCUSSION

4.1 Summary of Available Evidence

Three studies met the inclusion criteria for this systematic review. All three RCTs were open-label, multi-group studies that enrolled patients with CHC G1 infection and assessed LDV/SOF with or without RBV. Despite the multi- group design, the primary comparisons in all three trials were to historical control SVR rates. In ION-1, treatment-naive patients were randomized to one of four groups: LDV/SOF for 12 weeks, LDV/SOF for 24 weeks, LDV/SOF + RBV for 12 weeks, and LDV/SOF + RBV for 24 weeks. Cirrhosis was present in approximately 15% of patients in ION-1. ION-3 was a three-group trial that, while comparing each group to a historical control, also tested for non-inferiority between groups. Treatment groups in ION-3 were LDV/SOF for 12 weeks, LDV/SOF + RBV for eight weeks, and LDV/SOF for eight weeks in treatment-naive patients without cirrhosis. ION-2 had the same treatment groups as ION-1, but enrolled a treatment-experienced population with 20% of patients having cirrhosis.

The main limitation of the included trials was the lack of a treatment group consisting of an existing treatment regimen for CHC G1 infection. Comparison with a historical control could be biased due to differences in the distribution of potential confounders of effect. Furthermore, the lack of a comparator group limits the ability to compare the safety profile of LDV/SOF with existing regimens.

4.2 Interpretation of Results

4.2.1 Efficacy

The manufacturer is seeking reimbursement for LDV/SOF consistent with the Health Canada indication; i.e., in patients with CHC G1 infection. In patient group input submitted to CDR for this submission, outcomes of interest were cure of CHC infection, and with the cure, an associated reversal of cirrhosis and reduced risk of end-stage liver disease (APPENDIX 1: PATIENT INPUT SUMMARY).

In treatment-naive patients, the Health Canada–approved duration of 12 weeks for LDV/SOF was associated with high rates of successful treatment, with > 95% of patients achieving SVR12 in ION-1 and ION-3. These were all statistically significant, with an absolute difference of > 35% from the historical control rate used for comparison in the primary analysis. In the pre-specified subgroup analyses in the trial, SVR12 rates in patients with cirrhosis also remained high in the 12-week group, at 94% (APPENDIX 4: DETAILED OUTCOME DATA), although this subgroup was small (33 patients).

In ION-3, treatment-naive patients were exposed to a shorter treatment duration (eight weeks). This was found to be non-inferior to the 12-week regimen. The inclusion and exclusion criteria for this study were similar, aside from ION-1 allowing up to 20% of patients with cirrhosis. The Health Canada product monograph states that those patients with an HCV RNA viral load of less than 6 million IU/mL can be treated with eight weeks of LDV/SOF; however, the clinical expert contacted for this review noted that this cut-off is high.[29] ION-3 did not stratify patients based on this viral load cut-off, but a subgroup analysis reported in the Health Canada reviewer's report indicated higher relapse rates if the baseline HCV RNA viral load was greater than 6 million IU/mL in the eight-week group of LDV/SOF in ION-3.

In treatment-experienced patients, the SVR12 rates were also high, at 93% to 96% of patients in the 12-week groups and 99% in the 24-week groups of ION-2. The absolute difference was nearly 70% or more compared with the historical control rate of 25%. Patients with cirrhosis had SVR12 rates of 100% with 24 weeks of treatment, and 88% with 12 weeks. As in ION-1, the number of patients with cirrhosis was small, with approximately 21 patients per group with cirrhosis.

In all three trials, the addition of RBV appeared to provide no additional benefit to achieve SVR12, although it can only be confirmed to be non-inferior to an equivalent treatment group with no RBV in ION-3, as no between-group statistical comparison was completed in ION-1 or ION-2 for the primary outcome of SVR12. Health Canada has not approved concurrent use of RBV with LDV/SOF.

In the absence of a direct comparative trial, it is difficult to quantify the magnitude of benefit with LDV/SOF compared with existing DAA-containing regimens. The manufacturer submitted a network meta-analysis (NMA) for this purpose, in which the use of LDV/SOF was associated with higher odds of achieving SVR12 than PR-based DAA regimens. Traditionally, an NMA is conducted through the use of control groups to link active comparator groups to the network. However, due to the lack of non-LDV/SOF comparator groups, the ION trials could not be directly linked to the network; therefore, the manufacturer had to use alternative methods for this NMA. These essentially amounted to observational study-like comparisons between the ION cohorts and treatment groups from previous trials of PR-based regimens. An additional limitation was that aggregate data, rather than patient-level data, were incorporated in the NMA, precluding adjustment for potential confounders in the comparison of the ION trials with trials of PR-based regimens. Due to these limitations, the estimates reported in the NMA require cautious interpretation.

Multiple comparisons of HRQoL measures between beginning and end of treatment were statistically significant within treatment groups of all three trials. However, the clinical significance of these differences is not known, and no between-treatment differences were reported. Most statistical differences were associated with small changes from baseline and large standard deviations. Combined with the limitations of collecting these data in an open-label trial, the clinical significance of these results is not known. It should be noted that most values, particularly those in RBV-free groups, did not deteriorate through treatment, unlike what is typically seen with HRQoL scores from other DAA-based regimens that include PR.[9] This is not surprising given the adverse effect profile of PR-based regimens. However, in the absence of comparative HRQoL data for LDV/SOF with other regimens for CHC infection, the extent to which LDV/SOF is associated with improved quality of life over PR-based regimens remains uncertain.

Relapse rates were low in all trial groups. No data were available in the three pivotal trials for other clinical outcomes of interest described in the protocol.

4.2.2 Harms

Traditionally, AEs are quite common with CHC treatments and limit the success and willingness to initiate treatment. Patients described the AEs of existing therapies, particularly of Peg-IFN, to be severe and to have a significant impact on quality of life and their ability to function. Given the lack of non-LDV/SOF comparator groups in ION-1, -2, or -3, it is difficult to identify treatment-emergent AEs that can be attributed to the LDV/SOF regimen, or to assess comparative safety versus existing DAA-containing regimens. While the overall rates of AEs were high, it should be noted that the reported rates of SAEs were quite low compared with existing treatments evaluated in the CADTH Therapeutic Review of CHC treatments.[9] The most common AEs were relatively mild and self-limiting compared with AEs known to be associated with PR-based regimens, and overall discontinuation rates due to AEs were lower than those seen in previous trials that included PR in the evaluated regimens.

While the most common AEs reported in the LDV/SOF groups were fatigue, headache, and nausea, more severe AEs were seen in groups that contained RBV. In RBV-containing groups, AEs known to be associated with RBV, including cough, pruritus, rash, insomnia, irritability, and anemia were more frequent than in groups that did not contain RBV. In the absence of an active comparator or placebo group, it is difficult to judge the extent to which these AEs may be associated with LDV/SOF. Hematologic abnormalities were infrequent aside from anemia associated with the RBV regimens, and did not signal a flag for hematologic AEs of note with LDV/SOF regimens that did not contain RBV.

Unfortunately, the manufacturer's NMA did not attempt to assess the comparative safety profile of LDV/SOF with other DAA-containing regimens, and considerable uncertainty therefore remains in this regard. Informal comparisons of AE rates across HCV trials are fraught with potential confounding; hence, they are of limited value. That being said, the incidence of AEs neared almost 100% in many trials that assessed older HCV regimens based on CADTH's Therapeutic Review of CHC Therapies, with withdrawal due to AEs reported more frequently than what was observed in the three ION trials.[9] Known AEs of interferon and RBV, including depression, influenza-like symptoms, rash, anemia, and neutropenia, were not reported or were reported at very low rates with LDV/SOF in the ION trials, but occurred frequently in trials of PR-based regimens. Fatigue, another common AE of PR, occurs in about half of patients with PR-based regimens, versus the 20% to 25% reported in with LDV/SOF. Neutropenia, often associated with interferon use, occurs at rates of 6% to 31% with PR, whereas it occurs in almost no patients with LDV/SOF. Anemia was sparsely reported in patients taking LDV/SOF without RBV, but up to half of patients experience anemia with older regimens. While fewer than 10% of patients on LDV/SOF report rash, anywhere from 8% to 50% report rash with older regimens.

5. CONCLUSIONS

LDV/SOF administered for the Health Canada–approved durations was associated with high rates of SVR12 in patients with G1 CHC infection, in both treatment-naive and treatment-experienced patients. These rates were statistically significantly higher than historical control rates for DAA-containing regimens. The addition of RBV to LDV/SOF did not appear to improve SVR12 rates. LDV/SOF appeared to be better tolerated in a number of respects compared with RBV-containing regimens in the three pivotal trials. There were no direct comparative trials of LDV/SOF with existing DAA-containing regimens. The manufacturer-submitted NMA showed higher SVR rates with LDV/SOF than with PR-based DAA regimens; however, significant methodological limitations were noted that reduce confidence in the reported effect estimates. This renders it difficult to estimate the incremental benefit on SVR of LDV/SOF compared with other regimens. HRQoL scales demonstrated mixed and marginal changes from baseline to end of therapy. Relapse rates were low throughout all the trials, although the trials have limited long-term follow-up. Although some of the characteristic AEs associated with PR appeared to occur less frequently among patients treated with LDV/SOF, the lack of comparative data against existing regimens for CHC infection makes it difficult to judge the relative safety profile of LDV/SOF.

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.

1. Brief Description of Patient Group(s) Supplying Input
Six patient groups submitted input.

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

The Gastrointestinal (GI) Society is a Canadian charitable organization committed to improving the lives of people with gastrointestinal and liver diseases by providing evidence-based information, organizing support groups, supporting research, advocating access to care, and promoting gastrointestinal health. The GI Society has received charitable donations, grants or sponsorships from pharmaceutical companies, including funds from Gilead in 2012. It declared no conflicts of interest in the preparation of this submission.

Canadian Treatment Action Council (CTAC) is a national non-governmental organization whose mandate is to address access to treatment, care, and support for people living with HIV or hepatitis C virus (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 Gilead and other pharmaceutical companies. CTAC made no statement with regards to possible conflicts of interest in the preparation of this submission.

Pacific Hepatitis C Network's mission is to strengthen the capacity of individuals and organizations throughout British Columbia to prevent HCV infections and improve the health and treatment outcomes of people with HCV. Its members include individuals at risk, exposed to, or concerned about HCV. Pacific Hepatitis C Network has received one-time funding from pharmaceutical companies other than Gilead. It declared no conflicts of interest in the preparation of this submission.

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, general hepatitis information, and encouraging testing among at-risk groups. HepCBC has received funding from pharmaceutical companies, including Gilead, to support its educational activities, and the author of this submission has received funding to attend conferences.

The Centre d'Aide aux Personnes Atteintes d'Hépatite C (CAPAHC) is a community resource in Quebec for persons with hepatitis C and coinfection with HIV. The organization has declared conflicts of interest with pharmaceutical companies, including Gilead.

2. Condition and Current Therapy-Related Information

The information for this section was gathered through interviews with patients affected by hepatitis C, nurse specialists, gastroenterologists, hepatologists, and pharmacists, as well as through online surveys.

HCV is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, cancer, liver failure, and even death. For those coinfected with HIV, liver disease progression may be exacerbated. Some patients have few or no symptoms, but others experience fatigue, general weakness, abdominal, muscle, or joint pain, itchiness, poor circulation, constipation, nausea, loss of appetite, headaches, disrupted sleep, and jaundice. In some patients, the disease affects their cognitive functions such that they find it difficult to function, as their thinking, understanding, memory, or focus may be impeded. Fatigue and other symptoms may be severe, and can limit patients' ability to work, manage their home, care for family members, and maintain friendships.

Patients must cope with the stigma associated with HCV, and are often reluctant to disclose their HCV status for fear of rejection, discrimination, or ostracism. The social stigma, fear of spreading the infection, and uncertainty regarding their future health exact a high emotional toll on patients that may lead to depression, anxiety, loss of hope, and social isolation. Often marriages and other personal relationships cannot survive the strain. To patients, a cure means freedom from debilitating fatigue and stigma-centred fear, and optimism about their health.

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 is up to 48 weeks in duration and may include boceprevir (BOC) or telaprevir (TEL). Adverse effects (AEs) can be severe and debilitating, such as extreme fatigue, anemia, depression, anxiety, mood swings, rashes, headaches, chills, nausea, weight loss, suppressed appetite, hair loss, and joint pain. In addition, some triple-therapy regimens require patients to take up to 20 pills throughout the day, with specific food requirements, and have adverse drug interactions with antiretroviral therapies. Patients have no way of knowing whether the treatments will be successful or if their efforts to complete therapy and endure the side effects will be worth it. AEs of treatment may have an impact on patients' ability to continue working and to manage their household or child care. Many patients have contraindications or cannot tolerate interferon, thus are ineligible for interferon-based regimens. Injections associated with interferon can be a triggering factor and source of anxiety for those who have a history of injection drug use. Those who have failed interferon-based treatments have few treatment options.

3. Related Information About the Drug Being Reviewed

The expectations for ledipasvir/sofosbuvir (LDV/SOF) are that it would address a large gap and unmet patient need. There is currently no treatment available for patients who have a null response or relapse with standard therapies. Due to its low toxicity and lack of drug interactions, it is expected that LDV/SOF will open up treatment to patients who had contraindications to, or could not tolerate, interferon-based treatments, such as those with HIV coinfection, autoimmune conditions, psychiatric conditions, chronic anemia, or renal or liver transplant patients. Patients also have high expectations of a cure with LDV/SOF. With a cure, they expect their cirrhosis will reverse, and their risk of end-stage liver disease will be reduced. Some may be able to return to work, and their quality of life will improve.

LDV/SOF has advantages over current treatments: it is taken as one pill a day with no stringent food requirements; it is interferon-free; and treatment lasts for as few as eight to 12 weeks, further minimizing potential side effects. LDV/SOF also has high cure rates, which, along with affordability and interferon-free therapy, is the most important treatment-related factor reported by patients. Decreasing treatment time is a priority for patients and health care providers due to its impact on adherence, the burden of side effects, and to expedite patients' return to their normal lives.

Based on feedback from individuals who have experience with LDV/SOF, the treatment is easy to administer and tolerate. Two patients' viral count was 0 at or before the end of treatment. Side effects were minimal (abdominal pain, anemia, fatigue, and rash) and were more manageable than expected or compared with previous treatments. One patient reported that during treatment, he began to think more clearly and to feel happy, alive, and hopeful — feelings he had not experienced for years. He was able to return to work and his liver fibrosis improved. Physicians who have treated patients with LDV/SOF report that it is easier to use, with minimal side effects, and allows patients to be more productive during therapy, with fewer psychiatric concerns than are associated with interferon.

4. Additional Information

Low socioeconomic status is a risk factor for hepatitis C; thus, those most likely to be affected are least likely to be able to afford the new treatments. There are concerns that this treatment will not be accessible because it is either not covered by public drug plans or because the criteria for coverage will limit access. Coverage criteria may require patients to undergo and fail very challenging standard treatments before having access to LDV/SOF. Delaying treatment until liver disease is more advanced affects patients' physical and mental well-being. It is frustrating for individuals, especially those who are experiencing multiple barriers, to be told that they are not sick enough to qualify for treatment. Patients worry about the liver damage that may be caused by delaying treatment. The sooner a person is effectively treated (i.e., cured), the less chance they have of inadvertently infecting someone else. Improved treatments for hepatitis C have the potential to reduce social system and health care costs for patients with severe liver disease. Delays in the funding decision process could mean that time will run out for some patients.

APPENDIX 2: LITERATURE SEARCH STRATEGY

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:	October 21, 2014
Alerts:	Weekly search updates until April 15, 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were 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
MeSH	Medical 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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
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

MULTI-DATABASE STRATEGY

#	Searches
1	(Sovaldi* or sofosbuvir* or GI 7977 or GI7977 or GS-7977 or GS7977 or PSI 7977 or PSI7977 or WJ6CA3ZU8B or Virunon* or PSI 7851 or PSI7851 or PSI 7976 or PSI7976 or 1190307-88-0).ti,ot,ab,sh,hw,rn,nm.
2	(ledipasvir* or GS 5885 or GS-5885 or GS5885 or 013TE6E4WV or WHO 9796 or 1256388-51-8).ti,ot,ab,sh,hw,rn,nm.
3	1 and 2
4	3 use pmez
5	*sofosbuvir/
6	(Sovaldi* or sofosbuvir* or GI 7977 or GI7977 or GS-7977 or GS7977 or PSI 7977 or PSI7977 or WJ6CA3ZU8B or Virunon* or PSI 7851 or PSI7851 or PSI 7976 or PSI7976).ti,ab.
7	5 or 6
8	*ledipasvir/

MULTI-DATABASE STRATEGY	
#	**Searches**
9	(ledipasvir* or GS 5885 or GS-5885 or GS5885 or 013TE6E4WV or WHO 9796).ti,ab.
10	8 or 9
11	7 and 10
12	11 use oemezd
13	12 not conference abstract.pt.
14	4 or 13
15	harvoni.ti,ab.
16	14 or 15
17	remove duplicates from 16

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types 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

Dates for Search:	October 2014
Keywords:	Harvoni (ledipasvir/sofosbuvir), hepatitis C
Limits:	No date or language limits used

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
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV G1 infection. Gastroenterology. 2014 March;146(3):736-43.[30]	Phase 2 Study
Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with G1 hepatitis C virus infection (LONESTAR): an open-label, randomized, phase 2 trial. Lancet. 2014 February 8;383(9916):515-23.[31]	Phase 2 Study
Lawitz E, Poordad FF, Pang PS. Erratum: Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with G1 hepatitis C virus infection (LONESTAR): an open-label, randomized, phase 2 trial (Lancet (2014) 383 (515-23)). The Lancet. 2014;383(9920):870.[32]	Phase 2 Study
Gentile I, Borgia G. Ledipasvir/Sofosbuvir administration achieves very high rate of viral clearance in patients with HCV G1 infection without cirrhosis, regardless of ribavirin co-administration or length of treatment. Evid Based Med. 2014 July 15.[33]	Review Article
Yau AH, Yoshida EM. Hepatitis C drugs: The end of the pegylated interferon era and the emergence of all-oral interferon-free antiviral regimens: A concise review. Can J Gastroenterol Hepatol. 2014 Sep;28(8):445-51.[34]	Review Article
Luetkemeyer AF, Havlir DV, Currier JS. CROI 2014: viral hepatitis and complications of HIV disease and antiretroviral therapy. Top Antivir Med [Internet]. 2014 May [cited 2014 November 6];22(2):602-15.[35]	Review Article
Feld JJ. Interferon-free strategies with a nucleoside/nucleotide analogue. Semin Liver Dis [Internet]. 2014 February [cited 2014 Nov 6];34(1):37-46.[36]	Review Article
Pol S, Vallet-Pichard A, Corouge M. Treatment of hepatitis C virus genotype 3-infection. Liver Int [Internet]. 2014 February [cited 2014 Nov 6];34 Suppl 1:18-23.[37]	Review Article

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 9: SUBGROUP OUTCOME DATA FOR PIVOTAL TRIALS

	ION-1 Treatment-Naive G1				ION-3 Treatment-Naive G1			ION-2 Treatment-Experienced G1			
	LDV/ SOF12 (N = 214)	LDV/SOF + RBV12 (N = 217)	LDV/ SOF24 (N = 217)	LDV/SOF + RBV24 (N = 217)	LDV/ SOF8	LDV/ SOF + RBV8	LDV/ SOF12	LDV/ SOF12	LDV/ SOF + RBV12	LDV/ SOF24	LDV/ SOF + RBV24
No cirrhosis, n											
SVR12, patients, n (%)	177/180 (98.3%)	178/184 (96.7%)	181/184 (98.4%)	179/181 (98.9%)	NA	NA	NA	83/87 (95.4%)	89/89 (100.0%)	86/87 (98.9%)	88/89 (98.9%)
95% CI	95.2% to 99.7%	93.0% to 98.8%	NR	NR	NA	NA	NA	88.6% to 98.7%	95.9% to 100.0%	93.8% to 100.0%	93.9% to 100.0%
Cirrhosis, n											
SVR12, patients, n (%)	32/34 (94.1%)	33/33 (100.0%)	31/33 (93.9%)	36/36 (100%)	NA	NA	NA	19/22 (86.4%)	18/22 (81.8%)	22/22 (100.0%)	22/22 (100.0%)
95% CI	80.3% to 99.3%	89.4% to 100.0%	NR	NR	NA	NA	NA	65.1% to 97.1%	59.7% to 94.8%	84.6% to 100.0%	84.6% to 100.0%
G1a, n											
SVR12, patients, n (%)	139/ 144 (96.5%)	143/148 (96.6%)	143/ 146 (97.9%)	141/143 (98.6%)	159/ 171 (93%)	159/172 (92.4%)	163/ 172 (94.8%)	82/86 (95.3%)	84/88 (95.5%)	84/85 (98.8%)	87/88 (98.9%)
95% CI	92.1% to 98.9%	92.3% to 98.9%	NR	NR	88.1% to 96.3%	87.4% to 95.9%	90.3 to 97.6%	88.5% to 98.7%	88.8% to 98.7%	93.6% to 100.0%	93.8% to 100.0%
G1b, n											
SVR12, patients, n (%)	66/66 (100.0%)	67/68 (98.5%)	66/68 (97.1%)	71/71 (100%)	42/43 (97.7%)	42/44 (95.5%)	43/44 (97.7%)	20/23 (87.0%)	23/23 (100.0%)	24/24 (100.0%)	23/23 (100.0%)
95% CI	94.6% to 100.0%	92.1% to 100.0%	NR	NR	87.7% to 99.9%	84.5% to 99.4%	88.0 to 99.9%	66.4% to 97.2%	85.2% to 100.0%	85.8% to 100.0%	85.2% to 100.0%

CI = confidence interval; G1a = genotype 1a; G1b = genotype 1b; LDV/SOF8 = ledipasvir/sofosbuvir x 8 weeks; LDV/SOF12 = ledipasvir/sofosbuvir x 12 weeks; LDV/SOF24 = ledipasvir/sofosbuvir x 24 weeks; LDV/SOF + RBV8 = ledipasvir/sofosbuvir plus ribavirin x 8 weeks; LDV/SOF + RBV12 = ledipasvir/sofosbuvir plus ribavirin x 12 weeks; LDV/SOF + RBV24 = ledipasvir/sofosbuvir plus ribavirin x 24 weeks; NA = not applicable; NR = not reported; SAE = serious adverse effect; SVR12 = sustained virologic response at 12 weeks.
Source: Clinical Study Reports for ION-1, -2, and -3;[10-12] published report for ION-1.[20]

TABLE 10: SUBGROUP DATA BY PRIOR TREATMENT EXPOSURE AND RESPONSE

	ION-2 Treatment-Experienced G1			
	LDV/SOF12	**LDV/SOF + RBV12**	**LDV/SOF24**	**LDV/SOF + RBV24**
Response to Prior HCV Therapy				
Relapse or breakthrough[a]				
SVR12, Patients, n/N (%)	57/60 (95.0%)	63/65 (96.9%)	60/60 (100%)	59/60 (98.3%)
95% CI	86.1% to 99.0%	89.3% to 99.6%)	94.0% to 100.0%	91.1% to 100.0%
Non-responder[b]				
SVR12, Patients, n/N (%)	45/49 (91.8%)	44/46 (95.7%)	48/49 (98.0%)	51/51 (100.0%)
95% CI	80.4% to 97.7%	85.2% to 99.5%	89.1% to 99.9%	93.0% to 100.0%
Prior HCV Therapy				
PI + PR				
SVR12, Patients, n/N (%)	62/66 (93.9%)	62/64 (96.9%)	49/50 (98.0%)	51/51 (100.0%)
95% CI	85.2% to 98.3%	89.2% to 99.6%	89.4% to 99.9%	93.0% to 100.0%
PR				
SVR12, Patients, n/N (%)	40/43 (93.0%)	45/47 (95.7%)	58/58 (100.0%)	58/59 (98.3%)
95% CI	80.9% to 98.5%	85.5% to 99.5%	93.8% to 100.0%	90.9% to 100.0%

CI = confidence interval; G1 = genotype 1; HCV = hepatitis C virus; LDV/SOF12 = ledipasvir/sofosbuvir x 12 weeks; LDV/SOF24 = ledipasvir/sofosbuvir x 24 weeks; LDV/SOF + RBV12 = ledipasvir/sofosbuvir plus ribavirin x 12 weeks; LDV/SOF + RBV24 = ledipasvir/sofosbuvir plus ribavirin x 24 weeks; RNA = ribonucleic acid; SVR12 = sustained virologic response 12 weeks after the end of treatment.

[a] Relapse or breakthrough included patients who achieved undetectable HCV RNA levels during treatment or within 4 weeks of the end of treatment, but did not achieve SVR.

[b] The non-responder subgroup included patients who did not achieve undetectable HCV RNA levels while on treatment.

Source: Clinical Study Reports.[12]

TABLE 11: RELAPSE RATES, SUBGROUP DATA BY BASELINE RIBONUCLEIC ACID

	ION-3 Treatment-Naive G1		
	LDV/SOF8	**LDV/SOF + RBV12**	**LDV/SOF12**
Relapse n/N (%)			
HCV RNA < 6 million IU/mL	2/123 (1.6%)	NR	2/131 (1.53%)
HCV RNA ≥ 6 million IU/mL	9/92 (9.8%)	NR	1/85 (1.2%)

G1 = genotype 1; HCV = hepatitis C virus; LDV/SOF8 = ledipasvir/sofosbuvir x 8 weeks; LDV/SOF12 = ledipasvir/sofosbuvir x 12 weeks; LDV/SOF + RBV12 = ledipasvir/sofosbuvir plus ribavirin x 12 weeks; RNA = ribonucleic acid.

Source: Health Canada Reviewer Report.[24]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To review the validity of sustained virologic response at 12 weeks (SVR12) as a surrogate for SVR at 24 weeks (SVR24) and to summarize the characteristics of the following patient-reported outcome instruments:

- Chronic Liver Disease Questionnaire – Hepatitis C (CLDQ-HCV)
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)
- Short-Form (36-Item) Health Survey (SF-36)
- Work Productivity and Activity Impairment – Hepatitis C (WPAI-Hep C).

Findings

Sustained Virologic Response

SVR24 is the standard primary end point for assessing response to drugs that treat chronic hepatitis C (CHC) infection.[38] However, SVR12 is an emerging outcome of interest, potentially providing a means for determining treatment response earlier in either randomized controlled trials (RCTs) or clinics. In 2013, the FDA published a paper that sought to determine the predictive value of SVR12 as a surrogate for SVR24.[38] The authors reviewed data submitted to the FDA (2002 to 2011) from 15 phase 2 and 3 studies that included various treatment durations of pegylated interferon (Peg-IFN) alfa-2a, Peg-IFN alfa-2b, albinterferon alfa-2b, telaprevir, and boceprevir. The majority of the 13,599 participants were genotype 1 (G1) (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.[38] The positive predictive value between SVR12 and SVR24 was 98.3% and the negative predictive value was 98.8%. Thus, 1.2% of patients would be falsely identified as not achieving SVR 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 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 ribonucleic acid (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.[38] They also stated that these conclusions should be applied with caution to direct-acting antiviral (DAA)–only regimens, considering that they were based on data from regimens containing interferon plus ribavirin (RBV).[38] Further monitoring of interferon-free clinical trials may be required to determine the appropriate end point.

A study published in 2010 also evaluated the relevance of SVR12 as a primary outcome.[39] This study included 781 patients with CHC; all had received pegylated interferon plus ribavirin. Of the 781 patients, 573 had an end-of-treatment response and were thus included in the analysis. Of the 409 patients who achieved SVR12, 408 went on to have SVR24.[39] 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.

Another study explored differences between SVR12 and SVR24 among treatment-naive G1 CHC patients who received pegylated interferon plus ribavirin (PR).[40] The authors pooled single-group data for Peg-IFN alfa-2a or alfa-2b and RBV from 35 clinical trials. Of these trials, only one study reported both SVR12 and SVR24. The proportion with an SVR12 or SVR24 was pooled across trials using a DerSimonian–Laird random-effects model. Data for SVR12, SVR24, and for each type of Peg-IFN were pooled separately. The authors also performed a Bayesian random-effects meta-regression of the proportion with SVR12 or SVR24, controlling for the type of Peg-IFN. The authors concluded that SVR12 was 5% to 6% higher than SVR24, although the credible intervals overlapped in the conventional meta-analysis, and in the Bayesian meta-regression, the credible intervals included the null value (SVR12 versus SVR24 relative risk 1.13; 95% credible interval, 0.99 to 1.26).[40] These findings should be interpreted with caution considering that they were based on single treatment group data. Naive pooling of single-group data is not an acceptable method to determine comparative efficacy, as it ignores the benefits of randomization and may therefore be subject to the same biases as a comparison of independent cohort studies. In addition, the analysis was limited to data from patients who received PR, and did not examine the concordance of SVR12 and SVR24 among those who received a DAA regimen.

Published analyses are not available to compare the concordance between SVR12 and SVR24. However, an abstract was presented at the November 2014 meeting of the American Association for the Study of Liver Diseases that analyzed pooled data from ION-1, ION-2, and ION-3.[25] From this analysis, 1,902 patients with SVR12 values were available, and 1,853 patients had SVR24 values available. For the 97% of patients with both SVR12 and SVR24 measurements available, no patients relapsed between weeks 12 and 24, for a 100% concordance rate between SVR12 and SVR24 and a 100% positive predictive value for SVR12. It is important to note that these data have not been published and the full study methodology and analysis are not yet available.

Chronic Liver Disease Questionnaire — Hepatitis C

The CLDQ is a health-related quality of life (HRQoL) instrument for patients with chronic liver disease. CLDQ includes 29 items divided into six domains: Abdominal Symptoms, Fatigue, Systemic Symptoms, Activity, Emotional Function, and Worry. For each item, the patient assigns a score of 1 (all the time) to 7 (none of the time). The domain score is divided by the number of items in the domain. Domain scores are presented on a 1 to 7 scale, with higher numbers indicating the best possible function.[41] In the paper by Younossi et al.,[41] the investigators stated that a change of 0.5 on the 1 to 7 scale would signify an important difference in questionnaire score; however, there was no indication that conventional methods for validating a minimal clinically important difference (MCID) were used.[42]

It appears that the CLDQ was subsequently amended for use in CHC patients. From abstracts, we could find that scores are based on a Likert scale from 0 (worst) to 7 (best) and measure Activity/Energy, Emotion, Worry, Systemic, and CLDQ-HCV Total Score.[43,44] No detailed information was available.

Three abstracts on convergent validity and one abstract on construct validity of CLDQ-HCV were identified.[43-46]

Convergent Validity

CLDQ-HCV was validated against the Fatigue Severity Scale (high score = more fatigue) in 100 consecutive healthy blood donors and 50 CHC patients.[45] Correlations between the Fatigue Severity Scale and CLDQ-HCV in the 100 healthy blood donors were as follows: Activity/ Energy, r = –0.65 (P = 0.0001); Emotion, r = –0.61 (P < 0.0001); Worry, r = –0.23 (P < 0.0001); Systemic, r = –0.39 (P < 0.0001); and Overall Score, r = 0.58 (P < 0.0001). Comparison of CLDQ-HCV scores between

blood donor patients and CHC patients showed statistically significant differences in HRQoL measured by Worry ($P < 0.0001$), Emotion ($P = 0.048$), and Overall Score ($P = 0.004$), with worse (lower) scores in CHC patients.[45]

CLDQ-HCV was validated against SF-36 in 50 hepatitis C patients. CLDQ-HCV Activity/Energy (A/E) domain and SF-36 vitality (VT) and physical functioning (PF) scales were used. Statistically significant correlations were shown (VT versus A/E, r = 0.84, $P < 0.0001$; VT versus PF, r = 0.48, $P < 0.0001$).[46]

In another abstract, CLDQ-HCV was validated against SF-36 in 63 hepatitis C patients and r values were obtained (Table 12).[44] All findings were statistically significant.

TABLE 12: CORRELATION BETWEEN VARIOUS DOMAINS OF CLDQ-HCV AND SHORT-FORM 36-ITEM

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

CLDQ-HCV = Chronic Liver Disease Questionnaire — Hepatitis C Virus; NR = not reported; SF-36 = Short-Form 36-Item Health Survey.
Source: Escheik et al.[44]

Construct Validity

One abstract presented data on the validation of CLDQ in 62 hepatitis C patients versus 100 healthy blood donors.[43] Hepatitis C patients received PR treatment. Hepatitis C patients had lower (worse) CLDQ-HCV Overall Scores at baseline compared with healthy controls (5.7 ± 0.7 versus 6.2 ± 0.5, $P < 0.0001$). Lower scores were also reported at baseline for Emotion and Worry in hepatitis C patients (5.6 ± 0.4 and 5.7 ± 0.9) compared with healthy controls (5.9 ± 0.4 and 6.9 ± 0.2), respectively. After four and 24 weeks of treatment, Overall Scores decreased (worsened) in hepatitis C patients (5.4 ± 0.9 and 5.7 ± 0.8), and increased after treatment discontinuation (6.3 ± 0.6). The CLDQ was able to differentiate between hepatitis C patients and healthy controls. The instrument was also sensitive to change over time.[43]

An MCID for CLDQ-HCV has not been estimated, although one abstract[43] cited an MCID of 0.5, perhaps in reference to the paper by Younossi et al.[41] mentioned above.

Functional Assessment of Chronic Illness Therapy — Fatigue

The Functional Assessment of Cancer Therapy (FACT) was originally developed and validated in cancer patients.[47] The FACIT measurement system was later derived from FACT and validated in patients with chronic conditions, such as multiple sclerosis and rheumatoid arthritis.[48] FACIT is based on a generic core questionnaire (FACT — General) that includes 27 items divided into four primary domains: physical,

social/family, emotional, and functional well-being.[48] The FACIT — Fatigue scale (FACIT-F) includes an additional 13-item scale assessing fatigue and its impact on daily activities. Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale (40 items in total), make up the total score, ranging from 0 (worst) to 160 (best).[49] No information on the validity of FACIT-F or its MCID in hepatitis C patients was found. The MCID for the FACT — General total score ranged from 3 to 7 points in cancer patients.[48]

Short-Form 36-Item Health Survey

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions (GH), and role limitations due to physical and emotional problems. SF-36 also provides two component summaries: the physical component summary (SF-36 PCS) and the mental component summary (SF-36 MCS). The SF-36 PCS, SF-36 MCS, and eight dimensions are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of SF-36, a change of 2 to 4 points in each dimension or 2 to 3 points in each component summary indicates a clinically meaningful improvement as determined by the patient.[50]

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

- A total of 15 studies with SF-36 were included that compared HRQoL in patients with compensated hepatitis C seropositivity versus healthy controls. All 15 studies provided cross-sectional group mean HRQoL differences stratified by hepatitis C status (the clinical anchor). Patients with hepatitis C scored lower on the various domains compared with healthy patients. The largest impact of the disease was on role physical, role emotional, and general health (Table 13).[51]
- A panel of experts was convened to indirectly estimate the MCID in hepatitis C based upon existing HRQoL data.[51] The panel consisted of three hepatologists and two HRQoL methodologists with expertise in chronic liver disease-specific HRQoL. Based on the results of the systematic review, the panel determined that the SF-36 vitality scale captures the HRQoL domain that is most relevant to patients with hepatitis C. Using a modified Delphi technique, the expert panel generated a mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale, with a corresponding effect size of 0.2 (range 0.15 to 0.25).[51] MCIDs for other dimensions or for the two component scores were not estimated. Of note, this study did not use the preferred methods to generate the MCID and it is unclear if the estimates represent values patients would identify as clinically important.

No MCID estimates in patients with CHC were found for the component scores or for domains other than vitality. It is unclear if the MCID estimates from other conditions or the general population are generalizable to HCV.

TABLE 13: HEPATITIS C PATIENT VERSUS HEALTHY CONTROL-WEIGHTED MEAN AND MEDIAN CROSS-SECTIONAL DIFFERENCE (15 STUDIES)

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

Work Productivity and Activity Impairment — Hepatitis C

The Work Productivity and Activity Impairment questionnaire measures the impact of a disease on work and daily activities.[52] The questionnaire elicits information on the number of days or hours missed from work, days or hours worked, days during which the patient found it challenging to perform work, and the extent to which the patient was limited at work (work impairment) during the previous seven days. The work impairment domain is the sum of impairment in work productivity due to absenteeism (productivity loss due to a health-related absence from work, including personal time off, sick days off work, duration of short- or long-term disability, or worker's compensation days) and impairment due to decreased productivity while at work (reduced performance or productivity while at work due to health reasons, including time not being on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work. The scores are presented as a percentage, with lower values indicating better quality of life.

One study, available only as an abstract, measured the content validity of WPAI in hepatitis C using cognitive debriefing interviews. A total of seven patients interviewed confirmed that the questionnaire was relevant, understandable, and easy to complete.[53]

An MCID for WPAI has not been identified for patients with CHC infection.

Summary

A review using individual patient data from 15 phase 2 and 3 studies (N = 13,599 participants), in which the majority were patients with G1 (N = 11,730), suggests that SVR12 is a reliable surrogate for SVR24. The authors suggest that SVR12 may become a new definition for SVR for regulatory approval. There are also preliminary data to indicate a high degree of concordance between SVR12 and SVR24 for patients treated with LDV/SOF.

Four instruments were used in the Harvoni trials to measure patient-reported outcomes in hepatitis C patients, including one disease-specific HRQoL questionnaire. The CLDQ-HCV has shown good convergent and construct validities. Limited information was found on the validity of the WPAI questionnaire. No information was found on the validity of FACIT-F in patients with CHC infection, nor was an MCID identified.

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

APPENDIX 6: APPRAISAL OF MANUFACTURER-SUBMITTED INDIRECT COMPARISON

Aim

This brief provides a summary and critical appraisal of the methods and main findings of the network meta-analysis (NMA) submitted by the manufacturer.[54] This NMA compared the clinical efficacy of ledipasvir plus sofosbuvir (LDV/SOF) with other treatments approved for use in Canada for treatment-naive chronic hepatitis C (CHC) G1 infected patients.

CADTH conducted a literature search and found no other indirect comparisons that compared LDV/SOF to another direct-acting antiviral (DAA) or pegylated interferon plus ribavirin (PR) regimen.

Summary of Network Meta-Analysis

Given the lack of RCT evidence directly comparing the DAAs approved for use in Canada, the manufacturer conducted an NMA to estimate the comparative efficacy of LDV/SOF with boceprevir (BOC), telaprevir (TEL), simeprevir (SIM), or SOF in combination with PR. The outcome assessed was SVR.

Methods

Inclusion criteria for the review consisted of the following: treatment-naive G1 CHC patients who were 18 years of age or older, treated with SIM, SOF, BOC, or TEL plus PR, PR, or LDV/SOF at specific dosing regimens (Table 14). The study designs included were RCTs that provided comparative (head-to-head) data or a single treatment group with one of the eligible interventions, or a single-group clinical trial that provided data on an intervention of interest. The outcome of interest was SVR at 12 or 24 weeks after the end of treatment. Trials enrolling patients with other genotypes were allowed if up to 15% had genotype 4 CHC and up to 5% had some other genotype.

TABLE 14: DOSING REGIMENS INCLUDED IN THE NETWORK META-ANALYSIS

Regimen (in weeks)	Reference	DAA dose	Peginterferon dose	Ribavirin dose
PR 1-4, BOC+PR 5-48	BOC + PR (SDT)	800 mg	P2a, 180 µg or P2b, 1.5 µg/kg	600-1400 mg
PR 1-4, BOC+PR 5-28 or BOC+PR 5-28 PR 5-48*	BOC + PR (RGT)	800 mg	P2a, 180 µg or P2b, 1.5 µg/kg	600-1400 mg
TEL+PR 1-12, PR 13-48	TEL + PR (SDT)	750 mg	P2a, 180 µg or P2b, 1.5 µg/kg	600-1400 mg
TEL+PR 1-12, PR 13-24 or PR 13-48**	TEL + PR (RGT)	750 mg	P2a, 180 µg or P2b, 1.5 µg/kg	600-1400 mg
SIM+PR 1-12, PR 13-24***	SIM + PR (SDT)	400 mg	P2a, 180 µg or P2b, 1.5 µg/kg	600-1400 mg
SIM+PR 1-12, PR 13-24 or PR 13-48	SIM + PR (RGT)	150 mg	P2a, 180 µg or P2b, 1.5 µg/kg	600-1400 mg
SOF+PR 1-12****	SOF + PR	400 mg	P2a, 180 µg or P2b, 1.5 µg/kg	600-1400 mg
SOF+PR 1-12, PR 13-24 or PR 13-48	SOF + PR	400 mg	P2a, 180 µg or P2b, 1.5 µg/kg	600-1400 mg
SOF+LDV 1-12*****	SOF + LDV	SOF 400 mg; LDV 90 mg	--	--
PR 1-48	PR	--	P2a, 180 µg or P2b, 1.5 µg/kg	600-1400 mg

Abbreviations: BOC (boceprevir); DAA (direct acting antiviral); LDV (ledipasvir); SIM (simeprevir); PR (peginterferon + ribavirin); SOF (sofosbuvir); SDT (standard-duration therapy); SVR (sustained virological response); RGT (Response-guided therapy); TEL (telaprevir).
*Although the label for BOC in treatment-naïve patients is PR 1-4, BOC+PR 5-28 or PR 1-4, BOC+PR 5-36, PR 37-48, no single RCT has assessed this regimen. A priori we were aware that the RCTs assessed PR 1-4, BOC+PR 5-28 or 5-48, and thus, we considered this BOC regimen eligible for our analysis; **Label for TEL in treatment-naïve patients; ***Label for SIM in treatment-naïve patients; ****Label for SOF in treatment-naïve patients; *****Submission for SOF + LDV.

Source: Network meta-analysis (NMA) submitted by the manufacturer.[54]

The authors analyzed data using three approaches, two of which incorporated single-group data into the models. Because the LDV/SOF clinical trials have no control group to link to the network (i.e., disconnected network), these studies require unconventional methods to conduct the NMA. In addition, two of the three clinical trials for SOF + PR were also single-group trials. All models used a random-effects Bayesian framework and modelled the log odds ratio and 95% credible intervals for each treatment comparison (Table 15).

TABLE 15: DESCRIPTION OF NETWORK META-ANALYSIS MODELS

Model	Conventional NMA	Modified NMA — Single-Group Data as Priors	Modified NMA — Direct Incorporation of Single-Group Data
Studies included	Head-to-head RCTs	Head-to-head RCTs and single-group data	Head-to-head RCTs and single-group data
Treatments	P2aR, P2bR, SOF, BOC, TEL, or SIM plus P2aR or P2bR	LDV/SOF, P2aR, P2bR SOF, BOC, TEL, or SIM plus P2aR or P2bR	LDV/SOF, P2aR, P2bR, SOF, BOC, TEL, or SIM plus P2aR or P2bR
Priors	Non-informative	Informative	Informative
Model modifications	NA	Pooled single-group data (proportion SVR, 95% CI) were used to generate informative prior distributions for the log OR of LDV/SOF versus P2aR, SOF + PR versus P2aR, and P2aR versus P2bR.	• The control group (i.e., PR) response was modelled as a random-effects parameter that allowed for variation between trials. The model included parameters to allow for differences in PR response for SVR12 and SVR24, as well as for P2aR and P2bR. Single-group data for P2aR and P2bR were included directly into the model and used to inform the overall PR response rate. • Single-group data for DAAs were directly incorporated into the model as compared with the overall control group SVR response. • Informative priors were generated using pooled single-group data for log OR for LDV/SOF versus P2aR, SOF + PR versus P2aR, and P2aR versus P2bR, effect modification of SVR12 versus SVR12 associated with PR, and the expected SVR12 for P2aR.
Sensitivity analyses	None	Variances of the prior distributions were multiplied by 2 and 4 to reduce precision.	None
Assessment of convergence	Not reported	Not reported	Not reported
Assessment of model fit	Not reported	Not reported	Not reported
Assessment of consistency	Not reported	Not reported	Not reported

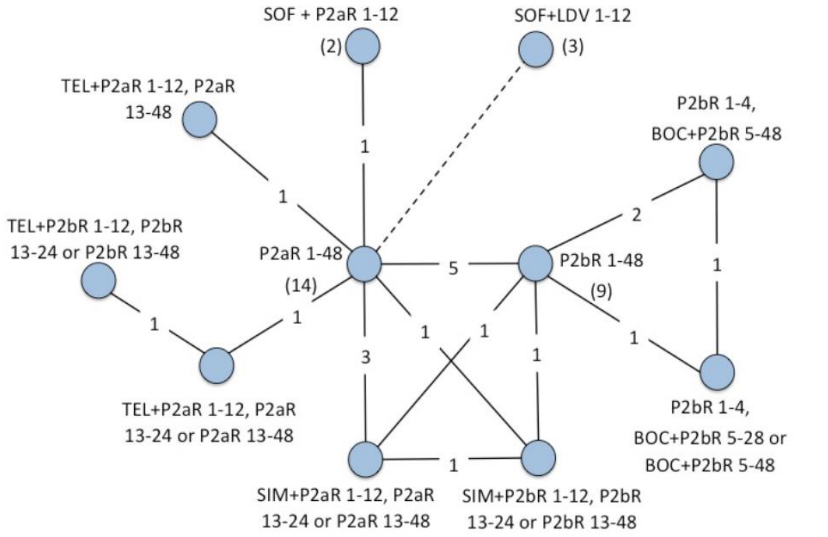
BOC = boceprevir; DAA = direct-acting antiviral; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; NMA = network meta-analysis; OR = odds ratio; PR = pegylated interferon plus ribavirin; P2aR = pegylated interferon 2a plus ribavirin; P2bR = pegylated interferon 2b plus ribavirin; RCT = randomized controlled trial; SIM = simeprevir; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after end of treatment; TEL = telaprevir.

Network Meta-Analysis Results

A total of 41 trials were included in the NMA: DAA + PR versus PR (eight RCTs); P2aR versus P2bR (four RCTs); LDV/SOF (three uncontrolled trials); SOF + PR (two uncontrolled trials); TEL + P2aR versus TEL + P2bR (one RCT); and single-group PR data (data from 23 trials that compared PR with older interferon controls). The authors pooled data from the uncontrolled SOF + PR studies with the SOF + PR versus PR study (PROTON) to increase network connectivity (methods for pooling not reported). The evidence network is provided in Figure 2.

The average age of patients per treatment group ranged from 42 to 55 years (age was not reported in three studies). Treatment groups varied in the proportion of males (27% to 82% across treatment groups, not reported in seven studies), with cirrhosis (0% to 27%, not reported in five trials), IL28B CC genotype (range 15% to 74%, not reported in 30 trials), and G1a (5% to 89%, not reported in 14 trials).

FIGURE 2: EVIDENCE NETWORK



Legend: Numbers on each connecting line represent the number of trials that included the corresponding comparison. Numbers in parentheses in regimen labels represent the number of single-arm trials for the corresponding treatment. Dashed edges represent treatments that are not connected to the network through head-to-head evidence.

BOC = boceprevir; P2aR = pegylated interferon 2a plus ribavirin; P2bR = pegylated interferon 2b plus ribavirin; SIM = simeprevir; SOF = sofosbuvir; LDV/SOF = ledipasvir/sofosbuvir; TEL = telaprevir.
Source: Network meta-analysis (NMA) submitted by the manufacturer.[54]

The results of the NMAs are presented in Table 17. Estimates were interpreted as statistically significantly different if the 95% credible interval (CrI) did not include the null value of 1. In the conventional NMA model, those who received P2bR were less likely to achieve SVR compared with those given P2aR (odds ratio [OR] 0.63; 95% CrI, 0.37 to 0.95). Four of the comparisons between DAA plus PR versus P2aR were statistically significant favouring the DAA (BOC, TEL, SIM, or SOF). The differences between SIM or BOC plus P2bR response-guided therapy (RGT), and for TEL plus P2aR 48-week therapy, compared with P2aR, did not reach statistical significance.

In the models that included single-group data, the odds of achieving an SVR were statistically significantly higher with LDV/SOF versus P2aR (direct inclusion of single-group data: OR 34.49; 95% CrI,

19.00 to 67.64; single-group data as informative prior distributions: OR 34.05; 95% CrI, 16.67 to 69.48). The differences between LDV/SOF and the DAA + PR regimes were also statistically significant favouring LDV/SOF in the model that included single-group data directly or as informative priors, including in the sensitivity analyses that penalized the prior distributions for precision by a factor of 2 or 4. The point estimates were generally similar across models, and the main variation was in the width of the credible intervals.

Critical Appraisal

The NMA was appraised using the National Institute for Health and Care Excellence Decision Support Unit Reviewer's Checklist.[55] The NMA did not satisfactorily meet the checklist's criteria on several items (Table 18).

The scope of the indirect comparison was limited to evaluating efficacy in treatment-naive CHC patients. The authors did not assess harms associated with therapies, nor did they assess efficacy and safety in patients previously treated with PR or another DAA regimen.

It appears that the authors did not conduct a systematic review to identify relevant studies. The methods used to screen and extract data from studies were not reported (i.e., there was no mention of independent screening by two reviewers). Moreover, it appears there was no assessment of the risk of bias in the included studies or of publication bias. That being said, the review has included the same DAA + PR clinical trials as identified in the recent CADTH Therapeutic Review, with a few exceptions.[9] The manufacturer-submitted NMA excluded some dosage regimens that were included in the CADTH review, namely TEL dosed every 12 hours and TEL for 12 weeks plus PR for 24 weeks; thus, clinical trials including these dosage regimens were excluded from the NMA.

Several reporting and methodological gaps were noted in the manufacturer's NMA. It was unclear which data were included in the analyses, as no SVR data from individual trials were reported. In addition, no information was reported related to model fit, convergence, or inconsistency. It appears there was no assessment of heterogeneity across trials. The model incorporated only two possible effect modifiers — SVR12 versus SVR24 and pegylated interferon type — and did not examine other important factors, such as fibrosis severity. Furthermore, the evidence[40] used to justify including SVR12 and SVR24 as an effect modifier of the control event rate was not robust. As discussed in Appendix 5, Validity of Outcome Measures, direct evidence from two studies (total N = 14,132)[38,39] demonstrated good concordance between SVR12 and SVR24 among patients receiving interferon-based regimens (positive predictive value of 98.3%; negative predictive value of 98.8%).

The lack of head-to-head RCTs for LDV/SOF necessitated the inclusion of data from three single-group studies into the NMA. The manufacturer, however, opted to also include data from 23 PR single-group studies and two single-group studies for SOF + PR despite the methodological limitations of including this type of study design in the NMA. Inclusion of single-group studies into a network likely diminishes the reliability and quality of the network as it requires naive, potentially confounded comparisons between estimates from single- group studies and estimates from other studies or historical control groups. This increases the potential to violate key underlying assumptions of NMA, namely transitivity. The decision to include all single-group evidence versus minimal single-group evidence was not adequately justified in the manufacturer's submission.

The manufacturer likely had access to patient-level data for certain comparators but opted to submit an aggregate level NMA including numerous single-group studies. Using patient-level data and approaches to adjust or match (e.g., through multivariable, propensity score methods)[56-58] the LDV/SOF group with other comparators would have resulted in more confidence that key fundamental assumptions underlying NMA, such as the transitivity assumption, were met. We have included a list of Gilead-sponsored studies (Table 14) where patient-level data could have been available and potentially used. Presentation of a series of patient-level comparisons for the treatments with multiple links in the network, by inserting one linkage at a time, would enhance trust in the methods. For example, it is possible to link LDV/SOF using the PR rate from a single study. Alternatively, one could link into the network using the pooled PR rate. There are numerous possibilities for assumed effect estimates and ways to link into the network that could have been attempted by the NMA authors.

TABLE 16: GILEAD-SPONSORED TRIALS OF SOFOSBUVIR IN TREATMENT-NAIVE G1 CHRONIC HEPATITIS C

Study	Intervention		Comparator	
	Drug	Duration (wks)	Drug	Duration (wks)
ION-1	LDV/SOF	12 or 24	--	
	LDV/SOF + RBV	12 or 24		
ION-3	LDV/SOF	8 or 12	--	
	LDV/SOF + RBV	8		
LONESTAR	LDV/SOF	8 or 12	--	
	LDV/SOF + RBV	8		
ELECTRON	LDV/SOF + RBV	6 or 12	--	
NEUTRINO	SOF + PR	12	--	
PROTON	SOF + PR	24 to 48 RGT[a]	PR	48
ATOMIC	SOF + PR	12 or 24	--	
	SOF + PR, SOF ± RBV	24		

CHC = chronic hepatitis C; G1 = genotype 1; LDV/SOF = ledipasvir/sofosbuvir; LDV/SOF + RBV = ledipasvir/sofosbuvir plus ribavirin; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RGT = response-guided therapy; SOF = sofosbuvir; wks = weeks.
[a] 12 weeks of SOF + PR, then 24 or 48 weeks of PR therapy depending upon virologic response.

The manufacturer opted to develop advanced methodological techniques for incorporating single-group evidence. In particular, they focused on developing statistical methods for incorporating single-group data as priors in the Bayesian framework. While methodologically interesting, this may not be the best approach for supporting decision-making. Even if the manufacturer was required to use aggregate level approaches, a range of SVR rates could have been presented for all possible linking treatments; i.e., results could have been reported based on average estimates as well as on various extreme scenario analyses for the linkage treatments. For example, one line of the table might have shown the mean response rate and mean N for one potential linkage treatment (e.g., P2aR), while another line of the table might include an extreme scenario analysis that selects the response rate and lowest N (to reduce precision and bias against LDV/SOF), for that linkage treatment or another one. Similarly, the manufacturer could have presented the most favourable finding for each potential linkage treatment. The table could include at least three scenarios for each potential linkage treatment and layer in data in a stepwise manner to enhance transparency. The user of the NMA would then have the ability to scan down the table and determine the relative efficacy of LDV/SOF based on what he or she believes to be the most probable scenario. For example, one might opt to consider the most conservative scenario to discourage the use of lower-quality comparative effectiveness evidence, or alternatively, the mean estimates might be considered the most reasonable reflection of reality.

In addition, the manufacturer focused solely on data at the study level. NMAs conducted for various subpopulations, in particular those stratified by degree of fibrosis, could have helped improve confidence that the overall results apply across the types of patients likely to be treated with LDV/SOF in clinical practice. Given the high cost of these drugs, stratified NMAs could have been used to conduct a stratified cost-effectiveness analysis, which would have provided a more detailed understanding of cost-effectiveness across various subpopulations.

Discussion

The willingness of regulatory bodies to accept uncontrolled studies as evidence to support approval for therapies for CHC infection has created additional challenges for evaluations of comparative efficacy and safety, particularly in estimating the magnitude of improvement versus existing treatments. As single-group studies do not have a direct, concurrent comparison group, their role in informing comparative effectiveness questions is not straightforward. Without a direct control group, it is not possible to determine what the control group's response would have been, if they had been treated. Although the manufacturer's NMA has shown two methods of incorporating single-group data and has generated relative efficacy estimates for LDV/SOF, the fact remains that these estimates are based on assumptions for the response rate for the "missing" control group.

The key assumption that underpins the validity of NMA is transitivity. Transitivity assumes that the indirect comparison validly estimates the unobserved head-to-head comparison.[59] Conceptually and epidemiologically, we can examine if a given evidence network is likely to meet this assumption by examining the control event rate, the distribution of effect modifiers, and the similarity of the linking treatments across studies, with the aim of determining whether participants could, in principle, have been randomized to any of the treatments in the network. With single-group trials, however, we are limited in our ability to assess transitivity and to detect potential sources of bias in the studies themselves. In effect, the inclusion of single-group studies in NMA necessitates the use of observational study-like comparisons. In the submitted NMA, rather than using the standard approaches used in observational studies (e.g., multivariate adjustment, propensity score matching) to adjust for covariates using patient-level data, the manufacturer pooled aggregate rates for comparator groups without adequately considering how similar patients in the pooled LDV/SOF group were to patients in other studies. Ensuring transitivity is met when only RCTs are included in NMA can be challenging enough, even though within-study comparisons theoretically balance for known and unknown confounders through randomization. When observational comparisons are included in NMA, the difficulty in verifying transitivity increases further; this is the case even if patient-level data and adjustment for known confounders are included in NMA, since there may be unknown or unmeasured confounders. Methods such as those employed in the manufacturer-submitted NMA in which aggregate level, single-group comparisons are included are most problematic with respect to determining whether the transitivity assumption is valid, since there is no adjustment at all for confounders. In essence, this approach is analogous to including unadjusted effect estimates in a meta-analysis of non-randomized studies.

Due to the aforementioned limitations, the quality of comparative clinical evidence available for LDV/SOF is of lower quality than is typically available in CADTH Common Drug Review submissions. Unconventional methods were required to incorporate the LDV/SOF data into the NMA, and these methods have yet to be validated. Although the NMA suggests that LDV/SOF is superior to other treatments for CHC, these estimates should be interpreted with caution.

Summary

The manufacturer submitted a Bayesian NMA which estimated the comparative efficacy of LDV/SOF with BOC, TEL, SIM, or SOF in combination with PR, or PR alone, in treatment-naive patients with G1 CHC infection. Data from 41 trials were incorporated into the model, including single-group data for PR, SOF + PR and LDV/SOF. Two novel methods were used to incorporate aggregate data from single-group studies into the NMA and to estimate the relative effects for LDV/SOF versus other CHC treatments. With both methods, the odds of achieving SVR were higher for LDV/SOF than for PR and for the other DAA + PR regimens.

Limitations of the model include the possibility that the transitivity assumption was not met; inclusion of supplementary single-group data that was not adequately justified; use of aggregate data for LDV/SOF instead of adjusted or matched individual patient data; lack of transparency and exploration of alternate values for SVR response for all the potential linkage treatments; and lack of stratified or sensitivity analyses to examine possible effect modifiers. Furthermore, the scope of the review was limited to assessment of efficacy, with no evaluation of relative harms among treatment-naive patients, and no examination of comparative safety or efficacy among treatment-experienced patients.

Given the limitations of the LDV/SOF studies, and the uncertain validity of the model, the findings of the NMA should be interpreted with caution.

TABLE 17: ODDS RATIOS AND 95% CREDIBLE INTERVALS OF SUSTAINED VIROLOGIC RESPONSE FOR EACH NETWORK META-ANALYSIS MODEL

Comparison	Direct inclusion of single arm evidence	Fully informative priors	Penalized prior precision (x2)	Penalized prior precision (x4)	Conventional non-informed
P2bR versus P2aR	0.80 (071, 0.91)	0.68 (0.56, 0.80)	0.68 (0.54, 0.84)	0.67 (0.50, 0.87)	0.63 (0.37, 0.95)
DAA combinations versus P2aR*					
BOC + P2bR (SDT)	2.87 (1.86, 4.49)	2.53 (1.51, 4.29)	2.53 (1.47, 4.33)	2.53 (1.43, 4.36)	2.42 (1.02, 5.23)
BOC + P2bR (RGT)	2.36 (1.40, 3.99)	2.08 (1.11, 3.84)	2.09 (1.08, 3.87)	2.09 (1.06, 3.91)	1.99 (0.71, 4.89)
TEL + P2aR (SDT)	2.56 (1.22, 5.41)	1.99 (0.82, 4.74)	2.00 (0.81, 4.75)	1.98 (0.80, 4.79)	1.87 (0.55, 5.63)
TEL + P2aR (RGT)	3.68 (2.12, 6.37)	3.80 (2.02, 7.22)	3.82 (2.00, 7.20)	3.80 (2.02, 7.16)	3.80 (1.53, 9.26)
SIM + P2aR (RGT)	4.95 (3.39, 7.33)	3.77 (2.35, 6.12)	3.74 (2.34, 6.12)	3.75 (2.31, 6.03)	3.73 (2.04, 6.79)
SIM + P2bR (RGT)	3.42 (2.01, 5.90)	2.31 (1.06, 5.16)	2.31 (1.04, 5.16)	2.28 (1.06, 5.08)	2.25 (0.84, 5.82)
SOF + P2aR	9.82 (6.16, 15.89)	9.35 (6.89, 12.71)	9.15 (5.97, 14.15)	8.97 (5.01, 15.83)	6.59 (1.51, 31.06)
SOF + LDV	34.49 (19.00, 67.64)	34.05 (16.67, 69.48)	33.83 (12.44, 93.35)	33.99 (8.12, 138.7)	--
SOF + P2aR versus other DAA combinations*					
BOC + P2bR (SDT)	3.42 (1.81, 6.47)	3.69 (2.02, 6.71)	3.62 (1.82, 7.27)	3.53 (1.60, 7.94)	2.73 (0.53, 16.11)
BOC + P2bR (RGT)	4.16 (2.08, 8.41)	4.50 (2.27, 9.02)	4.40 (2.07, 9.57)	4.31 (1.81, 10.42)	3.35 (0.60, 21.87)
TEL + P2aR (SDT)	3.85 (1.61, 9.19)	4.69 (1.89, 12.06)	4.58 (1.75, 12.49)	4.53 (1.58, 13.27)	3.55 (0.57, 25.59)
TEL + P2aR (RGT)	2.67 (1.31, 5.54)	2.46 (1.21, 4.93)	2.40 (1.11, 5.16)	2.35 (1.00, 5.49)	1.73 (0.32, 10.35)
SIM + P2aR (RGT)	1.99 (1.08, 3.65)	2.48 (1.40, 4.34)	2.45 (1.29, 4.64)	2.38 (1.12, 5.09)	1.76 (0.36, 9.13)
SIM + P2bR (RGT)	2.88 (1.41, 5.85)	4.05 (1.71, 9.42)	3.98 (1.61, 9.85)	3.93 (1.45, 10.47)	2.94 (0.52, 18.52)
SOF + LDV	0.28 (0.13, 0.61)	0.28 (0.13, 0.60)	0.27 (0.09, 0.80)	0.26 (0.06, 1.23)	--
SOF + LDV versus other DAA combinations**					
BOC + P2bR (SDT)	12.08 (5.72, 26.45)	13.44 (5.62, 32.5)	13.40 (4.30, 42.1)	13.45 (2.85, 61.77)	--
BOC + P2bR (RGT)	14.65 (6.63, 34.08)	16.40 (6.48, 41.74)	16.32 (4.99, 54.16)	16.45 (3.38, 78.27)	--
TEL + P2aR (SDT)	13.54 (5.20, 36.25)	17.11 (5.49, 53.19)	17.02 (4.50, 65.25)	17.20 (3.15, 94.72)	--
TEL + P2aR (RGT)	9.42 (4.17, 21.93)	8.95 (3.43, 23.21)	8.90 (2.76, 28.80)	8.96 (1.88, 41.20)	--
TEL + P2bR (RGT)	9.65 (2.81, 33.01)	11.97 (2.33, 61.54)	12.17 (2.07, 70.89)	12.25 (1.58, 91.87)	--
SIM + P2aR (RGT)	6.98 (3.42, 15.10)	9.01 (3.82, 21.23)	9.04 (2.99, 27.52)	9.08 (1.98, 40.61)	--
SIM + P2bR (RGT)	10.12 (4.50, 23.68)	14.79 (5.06, 42.01)	14.76 (4.12, 53.00)	14.93 (2.92, 75.20)	--
SOF + P2aR	3.51 (1.64, 7.84)	3.64 (1.67, 7.95)	3.68 (1.25, 11.00)	3.80 (0.81, 17.59)	--

1) Abbreviations: BOC (boceprevir); DAA (direct acting antiviral); LDV (ledipasvir); SIM (simeprevir); P2aR (peginterferon alpha-2a + ribavirin); P2bR (peginterferon alpha-2b + ribavirin); SOF (sofosbuvir); SDT (standard-duration therapy); SVR (sustained virological response); RGT (response-guided therapy); TEL (telaprevir).
2) Bolded results are statistically significant at the 0.05 significance level.
* Odds ratios larger than 1.00 indicate superiority of a DAA combination.
** Odds ratios larger than 1.00 indicate superiority of SOF + P2aR.
*** Odds ratios larger than 1.00 indicate superiority of SOF + LDV.

Source: Network meta-analysis (NMA) submitted by the manufacturer.[54]

TABLE 18: CRITICAL APPRAISAL CHECKLIST

		Item Satisfactory?	Comments
A. DEFINITION OF THE DECISION PROBLEM			
A1. Target Population for Decision			
A1.1	*Has the target patient population for decision been clearly defined?*	Partial	The population is clearly defined (treatment-naive G1 CHC) but is incomplete. LDV/SOF is also indicated for treatment-experienced CHC patients.
A2. Comparators			
A2.1	*Decision Comparator Set: Have all the appropriate treatments in the decision been identified?*	Yes	Includes all Health Canada–approved treatments; however, limits were applied to the included dosing regimens that affected the data available in the network.
A2.2	*Synthesis Comparator Set: Are there additional treatments in the Synthesis Comparator Set that are not in the Decision Comparator Set? If so, is this adequately justified?*	Yes	No additional treatments were included in the synthesis set. Rather than using single-group PR data taken from RCTs comparing PR to older interferon therapies, the authors could have expanded the network to include these other interferon treatments and incorporated the comparative data for PR versus interferon using conventional NMA methods.
A3. Trial Inclusion/Exclusion			
A3.1	*Is the search strategy technically adequate and appropriately reported?*	Partial	It is unclear if study screening was done independently by two reviewers. The search included multiple databases and hand searching of abstracts. Unclear if grey literature sources were searched.
A3.2	*Have all trials involving at least two of the treatments in the Synthesis Comparator Set been included?*	No	Trials comparing different dosage regimens of TEL were not included (OPTIMIZE Buti 2014 excluded).
A3.3	*Have all trials reporting relevant outcomes been included?*	No	Restrictions to the TEL dosing regimens limited the SVR data available to the network (i.e., only single-group data for PR was included in the NMA from trials comparing TEL + PR to PR where the comparator was TEL 12 weeks plus PR 24 weeks; data for TEL every 12-hour dosing regimen excluded).
A3.4	*Have additional trials been included? If so, is this adequately justified?*	No	Additional single-group data for PR were included in the model without sufficient justification. The transitivity assumption (i.e., that the relative treatment effects are identical to or exchangeable with those in the target population) cannot be assessed for these single-group studies. Naive indirect comparison of single-group data (i.e., where randomization has not been preserved) may produce biased estimates of treatment effect. The authors should have conducted sensitivity analyses excluding the single-group data for

		Item Satisfactory?	Comments
			PR but still including data from the uncontrolled LDV/SOF trials.
A4. Treatment Definition			
A4.1	*Are all the treatment options restricted to specific doses and co-treatments, or have different doses and co-treatments been "lumped" together? If the latter, is it adequately justified?*	Partial	The model analyzed each dosing regimen for the DAAs as separate nodes, except for SOF. It appears that RGT regimes of SOF + PR were pooled with data from uncontrolled studies that used the Health Canada–approved dose (SOF + PR for 12 weeks) in order to link the single-group data into the model. It is unclear how these data were pooled and which models used the pooled estimates. The model also included separate nodes for the type of pegylated interferon (2a or 2b). While there is some evidence of a difference between interferons, response rates were not statistically significantly different.[9,60] Moreover, indirect comparisons focus on relative effects; the underlying control SVR from the PR group should not affect the estimated odds ratio. The authors could have conducted a sensitivity analysis with a simplified model that "lumped" the interferons, as others have done.[9,61,62]
A4.2	*Are there any additional modelling assumptions?*	Partial	The model assumed there were differences between SVR12 and SVR24 for patients who received PR. The data to support the discrepancy between SVR12 and SVR24 were based on an analysis of single-group data.[40] The findings from this analysis of single-group data were inconsistent with the direct evidence, which showed that SVR12 was an acceptable proxy for SVR24 with high positive predictive values for patients who receive PR or DAA+PR.[38,39]
A5. Trial Outcomes and Scale of Measurement Chosen for the Synthesis			
A5.1	*Where alternative outcomes are available, has the choice of outcome measure used in the synthesis been justified?*	Partial	SVR is an appropriate outcome to assess efficacy in CHC trials; however, the NMA did not address harms associated with therapy.
A5.2	*Have the assumptions behind the choice of scale been justified?*	No	Data are reported as odds ratios, which may be misinterpreted as a relative risk and would appear to inflate the treatment effect.
A6. Patient Population: Trials with Patients Outside the Target Population			
A6.1	*Do some trials include patients outside the target population? If so, is this adequately justified?*	Partial	The authors included studies that enrolled patients with other genotypes if limited to a small proportion of the total population (genotype 4 < 15% and other genotypes < 5%). This is a possible source of heterogeneity, since patients with other genotypes were excluded from DAA trials, but may have been included in older interferon studies.

		Item Satisfactory?	Comments
A6.2	*What assumptions are made about the impact, or lack of impact this may have on the relative treatment effects? Are they adequately justified?*	Partial	Authors assumed that enrolment of other genotypes had no impact on the findings. Genotypes 2 and 3 may be more likely to respond, and genotype 4 may show similar response to PR therapy, compared with those with G1 CHC. Not all DAAs are effective against genotypes 2 to 6, and thus the transitivity assumption may not hold (i.e., patients with genotypes 2 to 6 CHC would not have been eligible for randomization in all clinical trials).
A6.3	*Has an adjustment been made to account for these differences? If so, comment on the adequacy of the evidence presented in support of this adjustment, and on the need for a sensitivity analysis.*	No	No sensitivity analyses or adjustments were made to account for inclusion of other genotypes.
A7. Patient Population: Heterogeneity Within the Target Population			
A7.1	*Has there been a review of the literature concerning potential modifiers of treatment effect?*	No	Authors state that differences in SVR12 and SVR24 in the PR group, and variation in treatment response based on Peg-IFN type, are the two key effect modifiers. No literature search was conducted for other predictors of response. Genotype subtype, fibrosis severity, and the presence of Q80K polymorphism and IL28B genotype are considered clinically important effect modifiers for different therapies.
A7.2	*Are there apparent or potential differences between trials in their patient populations, albeit within the target population? If so, has this been adequately taken into account?*	No	Treatment groups varied in the proportion with factors associated with poorer treatment response, including cirrhosis (0% to 27% across treatment groups, not reported in five trials); IL28B CC genotype (range 15% to 74%, not reported in 30 trials); and G1a (5% to 89%, not reported in 14 trials). These factors were not adjusted for in the analyses and no sensitivity or subgroup analyses were conducted.
A8. Risk of Bias			
A8.1	*Is there a discussion of the biases to which these trials, or this ensemble of trials, are vulnerable?*	No	The authors did not assess each study's risk of bias related to selection, performance, detection, attrition, reporting, or other sources of bias.
A8.2	*If a bias risk was identified, was any adjustment made to the analysis and was this adequately justified?*	No	There was no adjustment for risk of bias.

		Item Satisfactory?	Comments
A9. Presentation of the Data			
A9.1	*Is there a clear table or diagram showing which data have been included in the base-case analysis?*	Partial	The authors present a network diagram and study characteristics, but no raw data tables for the individual trials. Estimates of the informative priors, which were calculated using single-group data, were not reported and thus cannot be assessed for validity.
A9.2	*Is there a clear table or diagram showing which data have been excluded and why?*	No	
B. METHODS OF ANALYSIS AND PRESENTATION OF RESULTS			
B1. Meta-Analytic Methods			
B1.1	*Is the statistical model clearly described?*	Partial	Although an explanation of the methods is provided, details on priors, convergence, and number of iterations were not supplied in the text.
B1.2	*Has the software implementation been documented?*	Yes	WinBUGS code is provided
B2. Heterogeneity in the Relative Treatment Effects			
B2.1	*Have numerical estimates been provided of the degree of heterogeneity in the relative treatment effects?*	No	The authors did not report the degree of heterogeneity across pairwise comparisons.
B2.2	*Has a justification been given for choice of random or fixed effect models? Should sensitivity analyses be considered?*	No	There was no justification for selecting a random-effects model; and no deviance information criterion statistics, residual deviance, or between-study variance reported for the various models.
B2.3	*Has there been adequate response to heterogeneity?*	No	Potential heterogeneity was largely ignored.
B2.4	*Does the extent of unexplained variation in relative treatment effects threaten the robustness of conclusions?*	No	Unable to assess.
B2.5	*Has the statistical heterogeneity between baseline arms been discussed?*	No	No data on baseline rate for the PR treatment groups were provided, and it appears that no examination of the similarity of baseline rates across trials was conducted. Furthermore, single-group data for PR groups were incorporated into the model without adequate justification.
B3. Baseline Model for Trial Outcomes			
B3.1	*Are baseline effects and relative effects estimated in the same model? If so, has this*		NA

		Item Satisfactory?	Comments
	been justified?		
B3.2	*Has the choice of studies to inform the baseline model been explained?*		NA
B4. Presentation of Results of Analyses of Trial Data			
B4.1	*Are the relative treatment effects (relative to a placebo or "standard" comparator) tabulated, alongside measures of between-study heterogeneity if a random effects model is used?*	No	Relative treatment effects (relative to a placebo or "standard" comparator) were not tabulated alongside measures of between-study heterogeneity.
B4.2	*Are the absolute effects on each treatment, as they are used in the CEA, reported?*	No	Relative odds ratio and 95% credible interval are reported only. Data for baseline rates required for CEA are not reported.
C. ISSUES SPECIFIC TO NETWORK SYNTHESIS			
C1. Adequacy of Information on Model Specification and Software Implementation			
C2. Multi-Arm Trials			
C2.1	*If there are multi-arm trials, have the correlations between the relative treatment effects been taken into account?*	Yes	Correlations have been taken into account using adjustment in NICE TSD series.
C3. Connected and Disconnected Networks			
C3.1	*Is the network of evidence based on randomized trials connected?*	No	Disconnected network due to lack of control group for LDV/SOF and SOF + PR trials.
C4. Inconsistency			
C4.1	*How many inconsistencies could there be in the network?*	None	Network contains loops. There appear to be 4 but it is not easy to determine exactly how many. There was no dataset provided and the figure does not report information on multi-group trials.
C4.2	*Are there any* a priori *reasons for concern that inconsistency might exist, due to systematic clinical differences between the patients in trials comparing treatments A and B, and the patients in trials comparing treatments A and C, etc.?*	Partial	Including data from older interferon trials (e.g., P2aR versus P2bR) may introduce inconsistency into the model. With the inclusion of single-group data, it is unclear if the transitivity assumption is met.
C4.3	*Have adequate checks for inconsistency been made?*	No	It appears that no assessment of inconsistency was conducted.

		Item Satisfactory?	Comments
C4.4	*If inconsistency was detected, what adjustments were made to the analysis, and how was this justified?*	No	Inconsistency was not assessed.

CEA = cost-effectiveness analysis; CHC = chronic hepatitis C; DAA = direct-acting antiviral; G1 = genotype 1; LDV/SOF = ledipasvir/sofosbuvir; NA = not applicable; NMA = network meta-analysis; P2aR = pegylated interferon 2a plus ribavirin; P2BR = pegylated interferon 2B plus ribavirin; Peg-IFN = pegylated interferon; PR = pegylated interferon plus ribavirin; RCT = randomized controlled trial; RGT = response-guided therapy; SOF + PR = sofosbuvir and pegylated interferon plus ribavirin; SVR = sustained virologic response; SVR12 or SVR24 = sustained virologic response at 12 or 24 weeks; TEL = telaprevir; TEL + PR = telaprevir and pegylated interferon plus ribavirin.

REFERENCES

1. Hepatitis C in Canada: 2005-2010 surveillance report. Executive summary [Internet]. Ottawa: Public Health Agency of Canada; 2012. [cited 2014 Dec 9]. Available from: http://www.phac-aspc.gc.ca/sti-its-surv-epi/hepc/surv-eng.php
2. Kamal SM. Acute hepatitis C: a systematic review. Am J Gastroenterol. 2008 May;103(5):1283-97.
3. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. Lancet. 2008 Jul 26;372(9635):321-32.
4. Maheshwari A, Thuluvath PJ. Management of acute hepatitis C. Clin Liver Dis. 2010 Feb;14(1):169-76.
5. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001 Sep 22;358(9286):958-65.
6. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002 Sep 26;347(13):975-82.
7. Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.
8. Myers RP, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, et al. Burden of disease and cost of chronic hepatitis C virus infection in Canada. Can J Gastroenterol Hepatol. 2014 May;28(5):243-50.
9. Canadian Agency for Drugs and Technologies in Health. Direct-acting antiviral agents for chronic hepatitis C genotype 1 [Internet]. Ottawa: CADTH; 2014 Oct. [cited 2014 Nov 18]. (CADTH therapeutic review, volume 2, issue 2b). Available from: http://www.cadth.ca/media/pdf/TR0007_HepC_ScienceReport_e.pdf
10. Clinical study report: a phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naive subjects with chronic genotype 1 HCV infection. GS-US-337-0102 (ION-1) [**CONFIDENTIAL** internal manufacturer's report]. Foster City (CA): Gilead Sciences, Inc.; 2014 Jan 8.
11. Clinical study report: a phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed-dose combination ± ribavirin for 8 weeks and sofosbuvir/ledipasvir fixed-dose combination for 12 weeks in treatment-naive subjects with chronic genotype 1 HCV infection. GS-US-337-0108 (ION-3) [**CONFIDENTIAL** internal manufacturer's report]. Foster City (CA): Gilead Sciences, Inc.; 2014 Jan 17.
12. Clinical study report: a phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-experienced subjects with chronic genotype 1 HCV infection. GS-US-337-0109 (ION-2) [**CONFIDENTIAL** internal manufacturer's report]. Foster City (CA): Gilead Sciences, Inc.; 2014 Jan 9.
13. Remis RS. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007: final report [Internet]. Ottawa: Public Health Agency of Canada; 2009. [cited 2014 Dec 9]. Available from: http://www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf
14. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74.
15. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010 Feb;138(2):513-21, 521.

16. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 May 16;368(20):1878-87.

17. Wu HX, Wu J, Wong T, Donaldson T, Dinner K, Andonov A, et al. Enhanced surveillance of newly acquired hepatitis C virus infection in Canada, 1998 to 2004. Scand J Infect Dis. 2006;38(6-7):482-9.

18. Centers for Disease Control and Prevention (CDC). Notifiable diseases/deaths in selected cities weekly information. MMWR Morb Mortal Wkly Rep [Internet]. 2009 May 22 [cited 2014 Dec 9];58(19):543-54. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5819md.htm

19. CDEC final recommendation: sofosbuvir (Sovaldi—Gilead Sciences Canada, Inc.). Indication: Chronic Hepatitis C Infection [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014 Aug 18. [cited 2014 Dec 19]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_sovaldi_august_20_2014.pdf

20. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014 May 15;370(20):1889-98.

21. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014 May 15;370(20):1879-88.

22. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17;370(16):1483-93.

23. CDR submission: [Pr]Harvoni™ (Ledipasvir/Sofosbuvir) Tablets 90 mg/400 mg. Company: Gilead Sciences Canada, Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2014 Sep 12.

24. Health Canada reviewer's report: Harvoni (ledispavir/sofosbuvir) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2014 Sep 26.

25. Bernstein DE, Mangia A, Brau N, Yang JC, Ma J. Concordance between SVR4, SVR12 and SVR24 in genotype 1 HCV-infected patients who received all oral fixed-dose combination ledipasvir/sofosbuvir with or without ribavirin in phase 3 clinical trials [abstract]. Hepatology. 2014;60(1 Suppl):1142A.

26. U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Guidance for industry chronic hepatitis C virus infection: developing direct-acting antiviral drugs for treatment (draft guidance) [Internet]. Silver Spring (MD): FDA; 2013 Oct. [cited 2014 Dec 19]. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf

27. Osinusi A, Townsend K, Nelson s, Kohli A, Gross C, Polis MA. Use of sofosbuvir/ledipasvir fixed dose combination for treatment of HCV genotype-1 in patients coinfected with HIV [abstract]. J Hepatol. 2014;60(1 Suppl):S7.

28. Manufacturer's comments on CDR pharmacoeconomic and clinical reviewers' reports on Ledipasvir/sofosbuvir (Harvoni™) [**CONFIDENTIAL** manufacturer's report]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2015 Jan 9.

29. [Pr]Harvoni™ (Ledipasvir/Sofosbuvir) Tablets 90 mg/400 mg [product monograph]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2014 Sep 3.

30. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology. 2014 Mar;146(3):736-43.

31. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014 Feb 8;383(9916):515-23.
32. Lawitz E, Poordad FF, Pang PS. Erratum: Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial (Lancet (2014) 383 (515-23)). The Lancet. 2014;383(9920):870.
33. Gentile I, Borgia G. Ledipasvir/Sofosbuvir administration achieves very high rate of viral clearance in patients with HCV genotype 1 infection without cirrhosis, regardless of ribavirin co-administration or length of treatment. Evid Based Med. 2014 Dec;19(6):223-4.
34. Yau AH, Yoshida EM. Hepatitis C drugs: The end of the pegylated interferon era and the emergence of all-oral interferon-free antiviral regimens: A concise review. Can J Gastroenterol Hepatol. 2014 Sep;28(8):445-51.
35. Luetkemeyer AF, Havlir DV, Currier JS. CROI 2014: viral hepatitis and complications of HIV disease and antiretroviral therapy. Top Antivir Med [Internet]. 2014 May [cited 2014 Nov 6];22(2):602-15. Available from: http://www.iasusa.org/sites/default/files/tam/22-2-602.pdf
36. Feld JJ. Interferon-free strategies with a nucleoside/nucleotide analogue. Semin Liver Dis [Internet]. 2014 Feb [cited 2014 Nov 6];34(1):37-46. Available from: https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0034-1371009.pdf
37. Pol S, Vallet-Pichard A, Corouge M. Treatment of hepatitis C virus genotype 3-infection. Liver Int [Internet]. 2014 Feb [cited 2014 Nov 6];34 Suppl 1:18-23. Available from: http://onlinelibrary.wiley.com/doi/10.1111/liv.12405/pdf
38. Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013 Jun;144(7):1450-5.
39. Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclere L, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology [Internet]. 2010 Apr [cited 2014 Nov 14];51(4):1122-6. Available from: http://onlinelibrary.wiley.com/doi/10.1002/hep.23444/pdf
40. Thorlund K, Druyts E, Mills EJ. SVR12 is higher than SVR24 in treatment-naïve hepatitis C genotype 1 patients treated with peginterferon plus ribavirin. Clin Epidemiol [Internet]. 2014 [cited 2014 Nov 3];6:49-58. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3897323
41. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut [Internet]. 1999 Aug [cited 2014 Nov 27];45(2):295-300. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1727607
42. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol. 2008 Feb;61(2):102-9.

43. Younossi ZM. The chronic liver disease questionnaire- hepatitis C (CLDQ-HCV): a sensitive and valid health related quality of life instrument [Internet]. Abstract presented at: 63rd Annual Meeting of the American Association for the Study of Liver Diseases; 2012 Nov 9; Boston. [cited 2014 Nov 27]. Available from: http://liverlearning.aasld.org/aasld/2012/thelivermeeting/23481/doctor.zobair.younossi.the.chronic.liver.disease.questionnaire-.hepatitis.c.html

44. Escheik C, Gerber L, Rover L, Arsalla Z, Otgonsuren M, Younossi Z. Validation of CLDQ-HCV as a health related quality of life (HRQL) instrument for patients with chronic hepatitis C (CH-C) [abstract]. Am J Gastroenterol. 2012;107:S159.

45. Moon J, Kallman J, Younoszai Z, Winter PM, Fang Y, Gerber L, et al. Validation of chronic liver disease-HCV version (CLDQ-HCV) with fatigue severity scale (FSS) [abstract]. Gastroenterology [Internet]. 2010 [cited 2014 Nov 27];140(5 Suppl 1):S461. Available from: http://www.gastrojournal.org/article/S0016-5085%2810%2963840-1/pdf

46. Price JK, Moon J, Winter PM, Nader F, Soni M, Fang Y, et al. Hemoglobin level is associated with the physical functioning, activity, energy, and vitality aspects of health-related quality of life in patients with chronic hepatitis C (CH-C) [abstract]. Gastroenterology [Internet]. 2011 [cited 2014 Nov 27];140(5 Suppl 1):S461. Available from: http://www.gastrojournal.org/article/S0016-5085(11)61896-9/pdf

47. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol [Internet]. 1993 Mar;11(3):570-9.

48. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes [Internet]. 2003 [cited 2014 Nov 27];1:79. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC317391

49. Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, et al. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2014 Aug;12(8):1349-59.

50. Ware J, Kosinkski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. Determining important differences in scores. In: User's manual for the SF-36v2 health survey. Lincoln (RI): Quality Metric Inc.; 2007.

51. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology. 2005 Apr;41(4):790-800.

52. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993;4(5):353-65.

53. Blackburn S, McCool R, Panter C, Young V, Peterson S, Mitchell L, et al. Interviews with patients with chronic hepatitis C (CHC) virus infection document unmet needs, content validity, and comprehension of pros for clinical trials [abstract]. Value Health [Internet]. 2013 May [cited 2014 Nov 27];16(3):A6. Available from: http://www.valueinhealthjournal.com/article/S1098-3015(13)00105-8/fulltext

54. Sofosbuvir/ledipasvir fixed-dose combination versus competing interventions for treatment-naïve genotype 1 hepatitis C virus: a network meta-analysis. In: CDR submission: [Pr]Harvoni™ (Ledipasvir/Sofosbuvir) Tablets 90 mg/400 mg. Company: Gilead Sciences Canada, Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2014 Aug 28.

55. Ades AE, Caldwell DM, Reken S, Welton NJ, Sutton AJ, Dias S. NICE DSU technical support document 7: evidence synthesis of treatment efficacy in decision making: a reviewer's checklist [Internet]. Sheffield, UK: University of Sheffield, Decision Support Unit; 2012. [cited 2014 Nov 14]. Available from: http://www.nicedsu.org.uk/TSD7%20reviewer%20checklist.final.08.05.12.pdf

56. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health. 2012 Sep;15(6):940-7.

57. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. PharmacoEconomics. 2010;28(10):935-45.

58. Di Lorenzo G, Casciano R, Malangone E, Buonerba C, Sherman S, Willet J, et al. An adjusted indirect comparison of everolimus and sorafenib therapy in sunitinib-refractory metastatic renal cell carcinoma patients using repeated matched samples. Expert Opin Pharmacother. 2011 Jul;12(10):1491-7.

59. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Research Synthesis Methods. 2012;3:80-97.

60. Druyts E, Mills EJ, Nachega J, O'Regan C, Cooper CL. Differences in clinical outcomes among hepatitis C genotype 1-infected patients treated with peginterferon alpha-2a or peginterferon alpha-2b plus ribavirin: a meta-analysis. Clin Exp Gastroenterol [Internet]. 2012 [cited 2014 Nov 14];5:11-21. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3304330

61. Druyts E, Lorenzi M, Toor K, Thorlund K, Mills EJ. Network meta-analysis of direct-acting antivirals in combination with peginterferon-ribavirin for previously untreated patients with hepatitis C genotype 1 infection. QJM. 2014 Sep 19.

62. Tice JA, Ollendorf DA, Pearson SD, Institute for Clinical & Economic Review. The comparative clinical effectiveness and value of simprevir and sofosbuvir in the treatment of chronic hepatitis C infection: a technology assessment: final report [Internet]. San Francisco: California Technology Assessment Forum; 2014 Apr 15. [cited 2014 Nov 18]. Available from: http://www.ctaf.org/sites/default/files/assessments/CTAF_Hep_C_Apr14_final.pdf