CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

SOFOSBUVIR / VELPATASVIR / VOXILAPREVIR (VOSEVI)

(Gilead Sciences Canada, Inc.)

Indication: Hepatitis C infection genotype 1 to 6

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CHC	chronic hepatitis C
CI	confidence interval
CDR	CADTH Common Drug Review
DAA	direct-acting antiviral agent
DB	double blind
DCV	daclatasvir
DSV	dasabuvir
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GP	glecaprevir/pibrentasvir
HCV	hepatitis C virus
HRQoL	health-related quality of life
IFN	interferon
ITT	Intention to treat
LDV	ledipasvir
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
MCID	minimal clinically important difference
MD	mean difference
mITT	modified intention to treat
NA	not applicable
NMA	network meta-analysis
NR	not reported
NS3/4A	nonstructural viral protein 3/4A
NS5A	nonstructural viral protein 5A
NS5B	nonstructural viral protein 5B (NS5B)
OBV	ombitasvir
pegIFN	pegylated interferon
PR	pegylated interferon plus ribavirin
PTV/r	paritaprevir/ritonavir
RAV	resistance-associated variant
RBV	ribavirin
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SF-36	36-Item Short Form Survey Instrument
SOF	sofosbuvir
SVR 12	sustained virologic response 12 weeks after the end of treatment

VEL	velpatasvir
VOL	voxilaprevir
ULN	upper limit of normal
WDAE	withdrawal due to adverse event
WPAI	Work Productivity and Activity Impairment Questionnaire

Drug	Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)
Indication	For the treatment of chronic hepatitis C virus (HCV) infection in adult patients, without cirrhosis or with compensated cirrhosis, who have: • genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing a nonstructural viral protein 5A inhibitor; or • genotype 1, 2, 3, or 4 infection and have been previously treated with an HCV regimen containing sofosbuvir without a nonstructural viral protein 5A inhibitor.
Reimbursement Request	As per indication
Manufacturer	Gilead Sciences Inc.

Executive Summary

Introduction

Hepatitis C virus (HCV) infection is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), liver failure, and hepatic encephalopathy. HCV is one of the most common diseases leading to liver transplantation in the US.[1,2] Patients report that symptoms are variable, and for some, the symptoms can be severe and limit patients' ability to work, manage their home, care for family members, and maintain relationships. In 2013, an estimated 250,000 Canadians had chronic HCV infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[3] There are six major HCV genotypes, of which genotype 1 infections are the most common in Canada (65%).[3] Genotypes 2 and 3 are the next most common, estimated to represent 14% and 20% of HCV infections in Canada, respectively.[3] Genotypes 4, 5, and 6 are less common in Canada and account for less than 1% of HCV cases.[3]

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is a single-tablet triple-combination product. SOF is a nucleotide analogue pan-genotypic nonstructural protein 5B (NS5B) polymerase inhibitor. VEL is a pan-genotypic HCV nonstructural viral protein 5A (NS5A) inhibitor. VOX is a pan-genotypic inhibitor of the nonstructural viral protein 3/4A (NS3/4A) protease. SOF/VEL/VOX is indicated for the treatment of chronic HCV infection in adult patients without cirrhosis or with compensated cirrhosis who are direct-acting antiviral agent (DAA) treatment experienced with regimens containing an NS5A inhibitor (genotype 1 to 6) or SOF without an NS5A inhibitor (genotype 1 to 4).[4] Each tablet contains 400 mg of SOF, 100 mg of VEL, and 100 mg of VOX, and the recommended dosage is one tablet once daily with food for 12 weeks.[4]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of a SOF/VEL/VOX (400 mg / 100 mg / 100 mg) single-tablet regimen for the treatment of chronic hepatitis C (CHC) genotype 1, 2, 3, 4, 5, and 6 infection in adults who are DAA treatment experienced.

Results and Interpretation

Included Studies

A total of two pivotal phase III clinical trials were included in this review (POLARIS-1 and POLARIS-4). Both trials were randomized and multi-centre. POLARIS-1 was double blind, while POLARIS-4 was open label. POLARIS-1 (N = 415) assessed the efficacy, safety, and tolerability of SOF/VEL/VOX for 12 weeks compared with placebo among patients with genotype 1, 2, 3, 4, 5, or 6 chronic HCV infection who had previously been treated with a DAA regimen containing an NS5A inhibitor. POLARIS-4 (N = 333) assessed the efficacy and safety of SOF/VEL/VOX and SOF/VEL for 12 weeks in DAA-experienced patients with genotype 1, 2, 3, or 4 chronic HCV infection who had not previously been treated with an NS5A inhibitor. Both trials compared the percentage of patients who achieved a sustained virologic response 12 weeks after the end of treatment (SVR 12) for SOF/VEL/VOX or SOF/VEL (POLARIS-4 only) versus a performance goal of SVR 12 equal to 85%.

The main limitation of the POLARIS-1 trial was the lack of an active treatment comparator group consisting of an existing treatment regimen for CHC. The POLARIS-4 trial was open label, and so awareness of treatment allocation might have influenced subjective measures such as health-related quality of life and reporting of adverse events (AEs). Both trials assigned some patients to SOF/VEL/VOX treatment groups non-randomly; the POLARIS-1 trial, only patients with genotype 1 HCV infection were randomized to receive SOF/VEL/VOX or placebo, while patients with genotype 2, 3, 4, 5, or 6 HCV infection were assigned to the SOF/VEL/VOX treatment group only. In the POLARIS-4 trial, patients with genotype 4 HCV infection were assigned to the SOF/VEL/VOX treatment group only, while patients with HCV genotype 1, 2, or 3 HCV infection were randomized in a 1:1 ratio into the SOF/VEL/VOX or SOF/VEL groups. The primary outcome in the POLARIS-1 and POLARIS-4 trials was compared versus a performance goal; it was unclear how this threshold was chosen. There is also currently another treatment (glecaprevir/pibrentasvir [GP]) that is indicated for the treatment of adult patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with an NS3/4A protease inhibitor (but not both classes of inhibitors). On the other hand, it is acknowledged that GP is a new product and it was not available during the design and conduct of the POLARIS-1 and POLARIS-4 trials. Patients with HIV coinfection were excluded from both trials. No patients who had undergone a transplant were included in the trials, and few patients with genotype 5 and 6 HCV infection were enrolled in the POLARIS-1 trial, although globally, the prevalence of these viral variants in most regions is low.

Efficacy

The manufacturer is seeking reimbursement for SOF/VEL/VOX consistent with the Health Canada indication, i.e., for the treatment of chronic HCV infection in adult patients without cirrhosis or with compensated cirrhosis who have genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor, or who have genotype 1, 2, 3, or 4 infection and have been previously treated with an HCV regimen containing SOF without an NS5A inhibitor.

In the POLARIS-1 study, which included patients with genotypes 1, 2, 3, 4, 5, or 6 chronic HCV infection who had previously been treated with a DAA regimens containing NS5A inhibitor, the Health Canada–approved regimen of SOF/VEL/VOX for 12 weeks resulted in an SVR 12 rate of 96.2% (95% CI, 93.1% to 98.2%), which was statistically superior relative

to the pre-specified performance goal of 85% ($P < 0.001$). No patients in the placebo 12-week group achieved SVR 12. Overall, 10 out of 263 patients (3.8%) in the SOF/VEL/VOX 12-week group did not achieve SVR 12.

In the POLARIS-1 trial, treatment with SOF/VEL/VOX resulted in SVR 12 rates that ranged from 90.9% to 100% in all subgroups. The SVR 12 rates in the SOF/VEL/VOX 12-week group were 93.4% (95% CI, 87.4% to 97.1%) in patients with cirrhosis, 94.9% (95%CI, 87.4% to 98.6%) in patients with genotype 3 HCV infection, and 92.9% (95% CI, 82.7% to 98.0%) in patients with genotype 3 HCV infection with cirrhosis (which is more difficult to treat effectively). The SVR 12 rates were higher than 93.8% regardless of prior DAA-class combinations (NS5A + NS5B inhibitor: 93.8% [95% CI, 88.9% to 97.0%], NS5A + NS3 inhibitor ± NS5B inhibitor: 100% [95% CI, 95.7% to 100.0%]), or specific regimens ([redacted]).

In the POLARIS-1 trial, there was a high prevalence of baseline resistance-associated variants (RAVs) among the enrolled DAA-experienced patients, particularly NS5A RAVs. It seems that the persistence of these NS5A RAVs had no impact on the efficacy of SOF/VEL/VOX in the POLARIS-1 trial. No patient who relapsed following 12 weeks of SOF/VEL/VOX developed treatment-emergent RAVs.

In the POLARIS-4 trial, which included DAA-experienced patients with genotype 1, 2, 3, or 4 chronic HCV infection who have not received an NS5A inhibitor, the Health Canada–approved regimen of SOF/VEL/VOX for 12 weeks resulted in an SVR 12 rate of 97.8% (95% CI, 94.5% to 99.4%), which was statistically superior relative to the pre-specified performance goal of 85% ($P < 0.001$). The SOF/VEL 12-week treatment group included in the POLARIS-4 trial, which was not receiving a Health Canada–approved regimen for the patient population, did not meet the primary efficacy end point, with an SVR 12 rate of 90.1% (95% CI, 84.1% to 94.3%) compared with the performance goal of 85% ($P = 0.092$), as the lower bound of the 95% CI crossed the pre-specified threshold. The study was not designed to compare between the SOF/VEL/VOX and SOF/VEL treatment groups.

In the POLARIS-4 trial, the SVR 12 rates in the SOF/VEL/VOX 12-week group ranged from > 95.7% to 100% across subgroups. Within this treatment group, 46.2% of patients had cirrhosis, 97.6% (95% CI, 91.7% to 99.7%) of whom achieved SVR 12. The SVR 12 rates were also high regardless of prior DAA experience. The majority of patients had prior DAA exposure to SOF or to SOF + simeprevir, and the SVR 12 rates for these patients were 97.7% (95% CI, 93.5% to 99.5%) and [redacted]% (95% CI, [redacted]% to [redacted]%), respectively. Seven of the 13 patients that did not achieve SVR 12 in the SOF/VEL 12-week group had genotype 3 HCV infection and cirrhosis; the SVR 12 rate in this subgroup was 76.7% (95% CI, 57.7% to 90.1%). For patients in the SOF/VEL/VOX 12-week group, 96.8% (95% CI, 83.3% to 99.9%) of patients with genotype 3 HCV infection and cirrhosis achieved SVR 12. The SVR 12 rates, overall and for most subgroups, were higher following 12 weeks of SOF/VEL/VOX treatment compared with 12 weeks of SOF/VEL treatment. In patients with genotype 1a HCV infection, the SVR 12 rates were 98.1% (95% CI, 90.1% to 100.0%) and 88.6% (95% CI, 75.4% to 96.2%) in the SOF/VEL/VOX 12-week and SOF/VEL 12-week groups, respectively. In patients with genotype 1b HCV infection, the SVR 12 rates were 95.8% (95% CI, 78.9% to 99.9%) and 95.5% (95% CI, 77.2% to 99.9%) in the SOF/VEL/VOX 12-week and SOF/VEL 12-week groups, respectively. In patients with genotype 2 HCV infection, the SVR 12 rates were 100.0% (95% CI, 88.8% to 100.0%) and 97.0% (95% CI, 84.2% to 99.9%) in the SOF/VEL/VOX 12-week and SOF/VEL 12-week groups, respectively. In patients with genotype 3 HCV infection, the SVR 12 rates were

96.3% (95% CI, 87.3% to 99.5%) and 84.6% (95% CI, 71.9% to 93.1%) in the SOF/VEL/VOX 12-week and SOF/VEL 12-week groups, respectively. For patients with genotype 4 HCV infection, 100% (95% CI, 82.4% to 100.0%) of patients in the SOF/VEL/VOX 12-week group achieved SVR 12. Among cirrhotic patients, the SVR 12 in the SOF/VEL/VOX 12-week group was also higher compared with that of the SOF/VEL 12-week group (97.6% [95% CI, 91.7% to 99.7%] versus 85.5% [95%CI, 75.0% to 92.8%]). However, no statistical comparison was undertaken between treatment groups.

In the POLARIS-4 trial, it seems that there was no impact of baseline RAVs on SVR 12 for patients in the SOF/VEL/VOX 12-week or SOF/VEL 12-week groups. The single patient who relapsed in the SOF/VEL/VOX 12-week group did not have any treatment-emergent RAVs. However, 10 of the 14 patients in the SOF/VEL 12-week group did have treatment-emergent RAVs, all of whom had NS5A variants at the Y93 position.

The CADTH Common Drug Review protocol also included subgroups by HIV or hepatitis B coinfection, renal insufficiency, decompensated liver disease, and liver transplant; however, such subgroup analyses were not undertaken because patients who would fall into each of these subgroups were excluded from the trial. As a result, the efficacy and safety of SOF/VEL/VOX in these subgroups of patients is still unknown.

The trials evaluated SVR 12, which is a key outcome; however, none was designed to assess longer-term outcomes, such as hepatic-related morbidity or mortality, which are important to patients. Both trials evaluated patient-reported outcomes as exploratory outcomes. The instruments used in both trials included the 36-Item Short Form Survey Instrument, the Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), the Functional Assessment of Chronic Illness Therapy-Fatigue, and the Work Productivity and Activity Impairment Questionnaire, Hepatitis C instrument. Between-group statistical comparisons were conducted; however, no statistically significant differences were detected between SOF/VEL/VOX and the placebo groups (except for the CLDQ-HCV at the final treatment visit) or SOF/VEL for the instruments tested. Patient-reported outcomes reported in the trials were difficult to interpret due to limitations in the data, including the open-label design (POLARIS-4) and differences between treatment groups for which the corresponding 95% confidence interval for the treatment difference was not estimated; therefore, it was not possible to judge if the difference between treatment groups was clinically meaningful. In addition, minimal clinically important differences (MCIDs) specific to CHC patient-reported outcomes are unknown, which also limits the ability to interpret these results.

Harms

The majority of patients experienced one or more AEs, with headache, fatigue, diarrhea and nausea reported most frequently among those who received SOF/VEL/VOX. In the double-blind, placebo-controlled trial, 78% and 70% of patients reported AEs in the SOF/VEL/VOX and placebo groups, respectively (POLARIS-1). Overall, 77%, and 74% of patients in the SOF/VEL/VOX and SOF/VEL12-week groups, respectively, reported an AE in the POLARIS-4 randomized controlled trial.

In the POLARIS-1 trial, the incidence of serious AEs (SAEs) was 4.6% in the placebo 12-week group, which was more than double that reported in the SOF/VEL/VOX 12-week group (1.9%). One patient in the placebo 12-week group experienced an AE that led to interruption of study drug dosing, and four patients permanently discontinued study drug due to AEs (one patient in the SOF/VEL/VOX 12-week group and three patients in the placebo 12-week group). No patients died during the study. In the SOF/VEL/VOX 12-week group, no patients

had grade 3 or 4 elevated alanine aminotransferase (ALT), compared with three patients with grade 3 or 4 ALT elevations in the placebo 12-week group. A grade 3 increase in total bilirubin was reported in one patient in the SOF/VEL/VOX 12-week group. There was no evidence of VOX-related hepatotoxicity.

In the POLARIS-4 trial, the incidences of SAEs were similar in the SOF/VEL/VOX 12-week and the SOF/VEL 12-week groups (at 2.2% and 2.6%, respectively). One patient in the SOF/VEL 12-week group experienced an AE leading to premature discontinuation of the study drug, and one patient in the SOF/VEL/VOX 12-week group died of an illicit drug overdose two days after the last dose of study drug. Only one grade 3 elevated ALT was observed in a patient in the SOF/VEL/VOX 12-week group. This patient also had baseline grade 3 increased total bilirubin and increased aspartate aminotransferase, and all of these abnormalities were likely explained by ongoing heavy alcohol use, per the investigator. No other grade 3 or 4 chemistry laboratory abnormalities of increased ALT or total bilirubin were observed in this study. There was no evidence of VOX-related hepatotoxicity.

Of the included trials, only the POLARIS-1 trial was double blind; thus, the reporting of AEs may have been influenced by the patient's knowledge of the treatment received in the open-label POLARIS-4 trial. The lack of an active control group in the POLARIS-1 trial is an important limitation to the available safety data. Moreover, the trials were not designed to assess the longer-term safety of SOF/VEL/VOX. All of the trials excluded patients with hepatitis B coinfection; thus, the trials provide no data on the risk of hepatitis B reactivation, which is listed as a warning on the product monograph.[4] SOF/VEL/VOX also has a number of potentially clinically important drug-drug interactions that can affect the risk of AEs or reduce the therapeutic effect of SOF/VEL/VOX.[4]

Potential Place in Therapy[1]

Significant progress has been made in the treatment of HCV around the world since 2014.[5] DAA treatment regimens have revolutionized the ability to provide safe and effective therapy to the majority of patients with HCV, with SVR rates of more than 90% for all genotypes and stages of liver disease.[5] However, there is a population of HCV patients for whom treatment with a DAA regimen was unsuccessful and there are few options for a cure. Currently, there is one Health Canada–approved DAA regimen available for use in patients who have failed prior DAA therapy; however, the treatment duration is 16 weeks.

SOF/VEL/VOX, has been recently approved by Health Canada and now meets that need for this population. SOF/VEL/VOX is a pan-genotypic DAA regimen and has been shown in several phase III studies to result in SVR in more than 95% of patients with previous DAA failure after 12 weeks of treatment with minimal side effects. Therefore, in clinical practice, SOF/VEL/VOX would be considered in patients with HCV with compensated liver disease (including compensated cirrhosis), regardless of genotype. who have failed a prior DAA regimen. Given that the ability to achieve SVR in the phase III trials was not related to the presence of resistant variants, no special diagnostic tests would be required prior to consideration of therapy.

Conclusions

A 12-week regimen of SOF/VEL/VOX was associated with a high percentage of patients achieving SVR 12, with point estimates of 96.2% in the POLARIS-1 trial, which included

1 This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

patients with genotypes 1, 2, 3, 4, 5, or 6 chronic HCV infection who had previously been treated with DAA regimens containing an NS5A inhibitor, and 97.8% in the POLARIS-4 trial, which included DAA-experienced patients with genotypes 1, 2, 3, or 4 HCV chronic HCV infection who had not received an NS5A inhibitor. High rates of SVR 12 were observed across several subgroups of interest. The SVR 12 rates for SOF/VEL/VOX in POLARIS-1 and POLARIS-4 were statistically superior relative to the pre-specified performance goal of 85%. The presence of baseline RAVs did not impact the treatment outcome in the SOF/VEL/VOX 12-week group.

HRQoL, fatigue, and work productivity were evaluated as exploratory outcomes in the trials using the SF-36, the CLDQ-HCV, the FACIT-F questionnaire, and the WPAI: Hepatitis C. No conclusions could be drawn for these outcomes due to limitations in the data, which included an open-label study design (in the case of the POLARIS-4 trial) and the analysis methods used. Headache, fatigue, diarrhea, and nausea were reported most frequently among those who received SOF/VEL/VOX. None of the trials was designed to assess longer-term outcomes such as hepatic-related morbidity or mortality, which are important to patients.

Overall, data from the POLARIS trials demonstrated that treatment with SOF/VEL/VOX for 12 weeks was effective in treating patients included in the studies, with no apparent serious safety signal over this time period.

The key limitation was the limited comparative data. In particular, there were no comparative data versus GP, which is indicated for patients previously treated with either a regimen of an NS5A inhibitor or an NS3/4A protease inhibitor (but not both classes of inhibitors); however, GP is limited to the treatment-experienced patients with genotype 1 HCV infection. Patients from important subgroups who may be more difficult to treat (e.g., those with HIV coinfection or who have had a liver transplant) were excluded from the trials, and thus the generalizability of the studies' findings to these patients may be limited. Data were scarce for those with genotype 5 and 6 HCV infection, although globally, the prevalence of these viral variants in most regions is low.

Table 1: Summary of Results

Outcome	POLARIS-1[a]		POLARIS-4	
	SOF/VEL/VOX 12 weeks	Placebo 12 weeks	SOF/VEL/VOX 12 weeks	SOF/VEL 12 weeks
	N = 263	N = 152	N = 182	N = 151
SVR 12 (Full analysis set)				
SVR 12 n/N (%) [95% CI]	253/263 (96.2) [93.1, 98.2]	0	178/182 (97.8) [94.5, 99.4]	136/151 (90.1) [84.1, 94.3]
P value (compared with performance goal of 85%)	0.001	NA	0.001	0.092
SVR 12 by Subgroup				
Genotype				
1	146/150 (97.3)[b]		76/78 (97.4)	60/66 (90.9)
1a	97/101 (96.0)		53/54 (98.1)	39/44 (88.6)
1b	45/45 (100)		23/24 (95.8)	21/22 (95.5)
2	5/5 (100)		31/31 (100.0)	32/33 (97.0)
3	74/78 (94.9)		52/54 (96.3)	44/52 (84.6)
4	20/22 (90.9)		19/19 (100.0)	0/0

Outcome	POLARIS-1[a]		POLARIS-4	
	SOF/VEL/VOX 12 weeks	Placebo 12 weeks	SOF/VEL/VOX 12 weeks	SOF/VEL 12 weeks
	N = 263	N = 152	N = 182	N = 151
5	1/1 (100)		0/0	0/0
6	6/6 (100)		0/0	0/0
Cirrhosis				
Yes	113/121 (93.4)		82/84 (97.6)	59/69 (85.5)
No	140/142 (98.6)		96/98 (98.0)	77/82 (93.9)
Prior HCV therapy, n/N (%)				
DAA naive	0/0		0/0	1/1 (100.0)
NS5B only	0/0		131/134 (97.8)	99/109 (90.8)
NS5B + NS3	0/0		45/46 (97.8)	33/38 (86.8)
NS5A + NS5B	151/161 (93.8)		0/0	0/0
NS5A + NS3 ± NS5B	83/83 (100)		0/0	0/0
NS5A ± other	18/18 (100)		0/0	0/0
Other	[redacted]		[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]
HCV RNA (IU/mL)				
<800,000	69/73 (94.5)		44/46 (95.7)	35/38 (92.1)
≥800,000	184/190 (96.8)		134/136 (98.5)	101/113 (89.4)
Adverse Events				
Any AE, n (%)	206 (78)	107 (70)	140 (76.9)	111 (73.5)
SAE, n (%)	5 (1.9)	7 (4.6)	4 (2.2)	4 (2.6)
Death, n (%)	0	0	2 (1.1)	0
AE leading to discontinuation of study drug, n (%)	1 (0.4)	3 (2.0)	0	1 (0.7)
Notable harms(s)				
Anemia	1 (0.4)	1 (0.7)	0	1 (0.7)
Pruritus	6 (2)	2 (1)	0	6 (4.0)
Increased bilirubin (grade 3)	1 (0.4)	0	0	0
Increased ALT (grade 3 or 4)	0	3 (2)	1 (0.5)	0
Hepatotoxicity	0	0	0	0
Hepatic decompensation or hepatic failure events	NR	NR	NR	NR
Hepatocellular carcinoma	1 (0.4)	0	0	0

AE = adverse event: ALT = alanine aminotransferase; CI = confidence interval; DAA = direct-acting antiviral agent; HCV- hepatitis C virus; NA = not applicable; NS3 = nonstructural protein 3; NS5A = nonstructural protein 5A; NS5B = nonstructural protein 5B; NR = not reported; RNA = ribonucleic acid; SAE = serious adverse events; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir; SVR 12 = sustained virologic response 12 weeks after the end of treatment.

[a] The placebo group was not presented because zero patients achieved virologic response.

[b] Four patients had genotype 1 that was not 1a or 1b. All four patients achieved SVR.

Source: Clinical Study Reports.[6,7]

Introduction

Disease Prevalence and Incidence

Hepatitis C virus (HCV) infection is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), liver failure, and hepatic encephalopathy. HCV is one of the most common diseases leading to liver transplantation in the US.[1,2] It is caused by an enveloped, single-stranded linear ribonucleic acid (RNA) virus of the Flaviviridae family. In 2013, an estimated 250,000 Canadians had chronic HCV infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[3] A total of 10,180 new cases of HCV were reported in Canada in 2012, mostly due to injection drug use.[8] Hepatitis C most commonly affects people over 30 years of age and disproportionately men, although the gender gap is narrowing.[8] Other populations at higher risk for HCV infection include federal inmates, men who have sex with men, street-involved youth, and Indigenous peoples.[9] There are six major HCV genotypes, and genotype 1 infections are the most common in Canada (65%).[3] Genotypes 2 and 3 are the next most common, estimated to represent 14% and 20% of HCV infections in Canada, respectively.[3] Genotypes 4, 5, and 6 are less common in Canada and account for fewer than 1% of HCV cases.[3]

Of those infected, approximately 25% clear the infection spontaneously (the range is 15% to 45%), and the remainder develop chronic infection.[10-12] Of those with chronic infection, 15% to 25% will develop progressive liver disease, end-stage liver disease, or HCC, or will require liver transplant.[13] Male gender, alcohol use, HIV, or hepatitis B coinfection, obesity, and increasing age are associated with an increased risk of liver disease progression.[5,13] While the incidence of HCV infection appears to be stable or declining in Canada (although there is an increased incidence in some areas of US), it is expected that liver-related morbidity and mortality will continue to increase over the coming decades, as those who are already infected age.[3,8,14-16] Patient groups report that the degree to which symptoms affect individuals is variable, ranging from no or minor symptoms to severe symptoms that can limit patients' ability to work, manage their home, care for family members, and maintain relationships.

Standards of Therapy

The treatment paradigm for HCV infection continues to evolve rapidly. Ongoing development of new direct-acting antiviral agents (DAAs) has brought a number of drugs to market in Canada (Table 3), including the first pan-genotypic regimen velpatasvir (VEL) plus sofosbuvir (SOF) (Epclusa).[17-25] The combination of ledipasvir and SOF (Harvoni) also has approval for genotype 1 to 6 HCV infection, as well as for adult liver transplant recipients or those with HIV coinfection (genotype 1 and 4) and genotype 1 patients with decompensated cirrhosis.[20] Other agents available include elbasvir plus grazoprevir (Zepatier), which may be used in patients with genotype 1 and 4 HCV infection, or in combination with SOF in patients with genotype 3 infection.[25] Ombitasvir/paritaprevir/ritonavir (Technivie) is approved for use in genotype 4 chronic hepatitis C (CHC) and in combination with dasabuvir for genotype 1 CHC (Holkira Pak).[21,24] Additional treatment options include asunaprevir (Sunvepra) and daclatasvir (Daklinza) for patients with genotype 1b HCV infection or daclatasvir with SOF for those with genotype 1 to 3 infection.[18,23] In the April 2017 update to the Infectious Disease Society of America and American Association for the Study of Liver Diseases guidelines, interferon- or pegylated interferon-based treatment regimens, the first generation

nonstructural viral protein 3/4A (NS3/4A) protease inhibitors (boceprevir, telaprevir, and simeprevir with pegylated interferon plus ribavirin [PR]), and SOF/RBV were no longer recommended.[5]

The two most recently approved regimens, glecaprevir/pibrentasvir (GP) and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX), are both pan-genotypic. GP is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of nonstructural viral protein 5A (NS5A) inhibitor or with an NS3/4A protease inhibitor (but not both classes of inhibitors).[17] The September 2017 update to the Infectious Disease Society of America/American Association for the Study of Liver Diseases guidelines recommended SOF/VEL/VOX for the treatment of genotype 1a, GP for the treatment of genotype 1 (regardless of subtype), and SOF/VEL for the treatment of genotype 1b in non-NS5A inhibitor, SOF–containing regimen experienced patients with or without compensated cirrhosis.[5] In patients with genotype 1 with or without compensated cirrhosis who are treatment experienced with a DAA NS5A inhibitor, both GP and SOF/VEL/VOX were recommended as treatment options.[5] In genotype 2 patients with or without compensated cirrhosis, who are treatment experienced with SOF plus RBV, both GP and SOF/VEL were recommended as treatment options.[5] In genotype 3 patients with or without compensated cirrhosis who are DAA treatment experienced (including NS5A inhibitors), SOF/VEL/VOX was the only recommended treatment option, and SOF/VEL/VOX plus weight-based RBV was the only recommended treatment for patients with NS5A inhibitor failure and cirrhosis.[5] In genotype 4, 5, or 6 patients with or without compensated cirrhosis who are DAA treatment experienced (including NS5A inhibitors), SOF/VEL/VOX was the only recommended treatment option.[5]

Drug

SOF/VEL/VOX is a pan-genotypic single-tablet regimen of sofosbuvir, velpatasvir, and voxilaprevir. Sofosbuvir is a nucleotide analogue pan-genotypic nonstructural viral protein 5B (NS5B) polymerase inhibitor. Velpatasvir is a pan-genotypic HCV NS5A inhibitor. Voxilaprevir is a pan-genotypic inhibitor of the NS3/4A protease. SOF/VEL/VOX is indicated for the treatment of chronic HCV infection in adult patients without cirrhosis or with compensated cirrhosis who are DAA treatment experienced with regimens containing an NS5A inhibitor (genotype 1 to 6) or SOF without an NS5A inhibitor (genotype 1 to 4).[4]

Each tablet contains 400 mg of SOF, 100 mg of VEL, and 100 mg of VOX. The recommended dosage is one tablet once daily with food for 12 weeks (Table 2).[4]

SOF/VEL/VOX is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). The product monograph states that the safety and efficacy of SOF/VEL/VOX has not been established in patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73m^2) or end-stage renal disease (ESRD) requiring hemodialysis, or in HCV patients co-infected with HIV, in HCV patients co-infected with hepatitis B virus, in patients awaiting liver transplantation, or in patients with recurrent HCV infection post-liver transplant.[4]

Table 2: Health Canada–Recommended Treatment Duration

Genotype	Patients Previously Treated with an HCV Regimen Containing:	Duration
1, 2, 3, 4, 5, or 6	An NS5A inhibitor[a]	12 weeks
1, 2, 3, or 4	Sofosbuvir without an NS5A inhibitor[b]	12 weeks

HCV = Hepatitis C virus; NS5A = nonstructural viral protein 5A.
a. In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.
b. In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: pegylated interferon, alfa/ribavirin, ribavirin, or HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir).
Source: Vosevi product monograph.[4]

Table 3: Key Characteristics of DAAs Approved for Use in Canada

Drug (Brand Name)	Mechanism of Action	Health Canada Indication	Serious Adverse Effects / Safety Issues
Sofosbuvir (Sovaldi)	HCV NS5B polymerase inhibitor. The NS5B polymerase is an RNA polymerase that is critical for the viral replication cycle.	Treatment of genotype 1 and genotype 4 CHC infection in combination with PR Treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin	Fatigue, headache, and insomnia
Sofosbuvir/Ledipasvir (Harvoni)	Ledipasvir is an HCV NS5A inhibitor. The NS5A protein is an essential component of HCV replicase, even though no known enzymatic function has been associated with it. Sofosbuvir is an NS5B polymerase inhibitor.	Treatment of CHC infection genotype 1 to 6 in adults with and without cirrhosis, including • genotype 1 and 4 CHC infection in adult liver transplant recipients without cirrhosis, or with compensated cirrhosis in combination with ribavirin; • genotype 1 and 4 CHC infection in adults with HIV coinfection, without cirrhosis, or with compensated cirrhosis; • genotype 1 CHC infection in adult patients with decompensated cirrhosis (Child-Pugh B or C) in combination with ribavirin; • genotype 3 CHC without cirrhosis or with compensated cirrhosis in combination with ribavirin • genotype 1, 2, 4, 5, and 6 without cirrhosis or with compensated cirrhosis. Treatment of CHC genotype 1 infection in pediatric patients ≥ 12 years of age without cirrhosis or with compensated cirrhosis	Fatigue and headache

Drug (Brand Name)	Mechanism of Action	Health Canada Indication	Serious Adverse Effects / Safety Issues
Sofosbuvir/Velpatasvir (Epclusa)	Velpatasvir is an HCV inhibitor targeting the HCV NS5A protein. Sofosbuvir is an NS5B polymerase inhibitor.	Treatment of all HCV genotypes in adult patients without cirrhosis and patients with compensated cirrhosis Treatment of all HCV genotypes in adult patients with decompensated cirrhosis in combination with ribavirin	Headache and fatigue
Daclatasvir (Daklinza)	Inhibitor of the NS5A replication complex	Treatment of CHC in adult patients with HCV genotypes 1, 2, or 3 with or without HIV coinfection, in combination with • sofosbuvir for patients without cirrhosis • sofosbuvir and ribavirin for patients with compensated (Child-Pugh class A) or decompensated cirrhosis (Child-Pugh class B and C) • sofosbuvir and ribavirin for patients with HCV recurrence after liver transplant	Headache and fatigue
Asunaprevir (Sunvepra)	HCV NS3/4A serine protease inhibitor, which inhibits viral replication	Treatment of CHC in adult patients with HCV genotypes 1 or 4 and compensated liver disease, including cirrhosis in combination with • Daclatasvir for genotype 1b HCV and • Daclatasvir, pegylated interferon alfa, and ribavirin for genotype 1 and 4 HCV	Headache and fatigue
Ombitasvir / paritaprevir /ritonavir and dasabuvir (Holkira Pak)	Ombitasvir: HCV NS5A inhibitor that inhibits viral replication Paritaprevir: HCV NS3/4A protease inhibitor that inhibits viral replication Dasabuvir: non-nucleoside polymerase inhibitor encoded by the NS5B gene that is essential for replication of the viral genome Ritonavir: pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir. It is not active against HCV.	Treatment of adults with genotype 1 chronic HCV infection, including those with compensated cirrhosis • with ribavirin in non-cirrhotic and cirrhotic patients with genotype 1a infection or • without ribavirin in non-cirrhotic and cirrhotic patients with genotype 1b infection	Fatigue, headache, nausea, pruritus, and insomnia
Ombitasvir/paritaprevir/ritonavir (Technivie)	Ombitasvir: HCV NS5A inhibitor that inhibits viral replication Paritaprevir: HCV NS3/4A protease inhibitor that inhibits viral replication	Alone or in combination with ribavirin for the treatment of adults with genotype 4 CHC virus infection, including those with compensated cirrhosis, who are	Fatigue, headache, nausea, pruritus, and insomnia

Drug (Brand Name)	Mechanism of Action	Health Canada Indication	Serious Adverse Effects / Safety Issues
	Ritonavir: pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir. It is not active against HCV.	either treatment naive or had been treated previously with PR	
Elbasvir/grazoprevir (Zepatier)	Elbasvir is an HCV NS5A inhibitor. Grazoprevir is an HCV NS3/4A protease inhibitor.	Alone or in combination with ribavirin for the treatment of genotype 1 or 4 CHC infection in adults In combination with sofosbuvir for the treatment of CHC genotype 3 infection in treatment naive adult patients	Nausea, headache, and fatigue
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)	Velpatasvir is an HCV NS5A inhibitor. Voxilaprevir is an NS3/4A protease inhibitor. Sofosbuvir is a NS5B polymerase inhibitor.	For the treatment of CHC in adult patients without cirrhosis or with compensated cirrhosis who have: • genotype 1, 2, 3, 4, 5, or 6 infection and have been treated previously with an HCV regimen containing an NS5A inhibitor; • genotype 1, 2, 3, or 4 infection and have been treated previously with an HCV regimen containing sofosbuvir without an NS5A inhibitor	Headache, fatigue, diarrhea, and nausea
Glecaprevir/pibrentasvir (Maviret)	Glecaprevir is an NS3/4A protease inhibitor, and pibrentasvir is NS5A inhibitor.	For the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or a NS3/4A protease inhibitor but not with both classes of inhibitors. (Includes patients with HIV coinfection)	Headache and fatigue

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; NS3/4A = nonstructural viral protein 3/4A; NS5A = nonstructural viral protein 5A; NS5B = nonstructural viral protein 5B; PR = pegylated interferon plus ribavirin; RNA = ribonucleic acid.
[a] Health Canada indication.
Source: Product monographs.[17-25]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of a SOF/VEL/VOX (400 mg / 100 mg / 100 mg) single-tablet regimen for the treatment of CHC genotype 1, 2, 3, 4, 5, and 6 infection in adults who are DAA treatment experienced.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adults with CHC genotype 1 through 6 who are DAA treatment experienced **Subpopulations:** • Treatment history (DAA-experienced NS5A ± DAAs [NS5A, NS5A + NS5B, NS5A + NS3 ± NS5B, NS5A ± other(s)], or DAA-experienced non-NS5A [non-NS5A ± DAAs, NS5B only, NS5B + NS3, or NS3 inhibitor]) • Fibrosis level • Cirrhosis • HIV coinfection • Hepatitis B coinfection • Genotype • Genotype subtype 1a or 1b • Renal insufficiency • Liver transplant • Decompensated liver disease • HCV RNA levels • Baseline NS5A or NS3 resistance variants
Intervention	Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg for 12 weeks[a] for adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis who have • genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor • genotype 1, 2, 3, or 4 infection that has been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
Comparators	**Genotype 1** • Glecaprevir/pibrentasvir • Ledipasvir/sofosbuvir • Daclatasvir/sofosbuvir ± ribavirin[b] • Asunaprevir/daclatasvir for genotype 1b[c] • Sofosbuvir/velpatasvir • Placebo or no treatment **Genotype 2** • Ledipasvir/sofosbuvir • Sofosbuvir/velpatasvir • Sofosbuvir/ribavirin • Daclatasvir/sofosbuvir ± ribavirin[b] • Placebo or no treatment

	Genotype 3 • Ledipasvir/sofosbuvir plus ribavirin • Sofosbuvir/velpatasvir • Sofosbuvir/ribavirin • Daclatasvir/sofosbuvir ± ribavirin[b] • Placebo or no treatment **Genotype 4** • Ledipasvir/sofosbuvir • Sofosbuvir/velpatasvir • Placebo or no treatment **Genotype 5** • Ledipasvir/sofosbuvir • Sofosbuvir/velpatasvir • Placebo or no treatment **Genotype 6** • Ledipasvir/sofosbuvir • Sofosbuvir/velpatasvir • Placebo or no treatment
Outcomes	**Key efficacy outcomes:** • Sustained virologic response[d] • Treatment failure • Virologic failure (i.e., on-treatment failure or relapse) • HRQoL[d] • Patient-reported symptoms (e.g., fatigue)[d] • Mortality (all cause and liver-related)[d] **Other efficacy outcomes:** • Hepatic-related morbidity outcomes (e.g., histological changes, hepatocellular carcinoma, liver failure, or liver transplant) • Work productivity **Harms outcomes:** AEs, SAEs, and WDAEs, Harms of special interest included nausea, fatigue, anemia, pruritus, headache, ALT elevations, elevated bilirubin, and hepatitis B reactivation.
Study Design	Published and unpublished Phase III RCTs

AE = adverse events ALT = alanine aminotransferase; CHC = chronic hepatitis C; DAA = direct-acting antiviral agent; DB = double blind; HRQoL= health-related quality of life; HCV = hepatitis C virus; NS3 = nonstructural viral protein 3; NS5A = nonstructural viral protein 5A; NS5B = nonstructural viral protein 5B; RCT = randomized controlled trial; RNA = ribonucleic acid; SAE = serious adverse event; WDAE = withdrawal due to adverse events.

[a] Health Canada–approved dosage regimens.

[b] Excludes patients with previous exposure to NS5A inhibitors.

[c] Patients who failed prior therapy with an interferon-based regimen.

[d] Outcomes identified as important based on patient input.

An information specialist using a peer-reviewed search strategy performed the literature search.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & 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 Medical Subject Headings, and keywords. The main search concept was a combination of three drug names.

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. See Appendix 2 for the detailed search strategies.

The initial search was completed on August 28, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on December 13, 2017. 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 (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), and 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 CADTH Common Drug Review (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 5; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (). The included studies are summarized in Table 5: Details of Included Studies and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

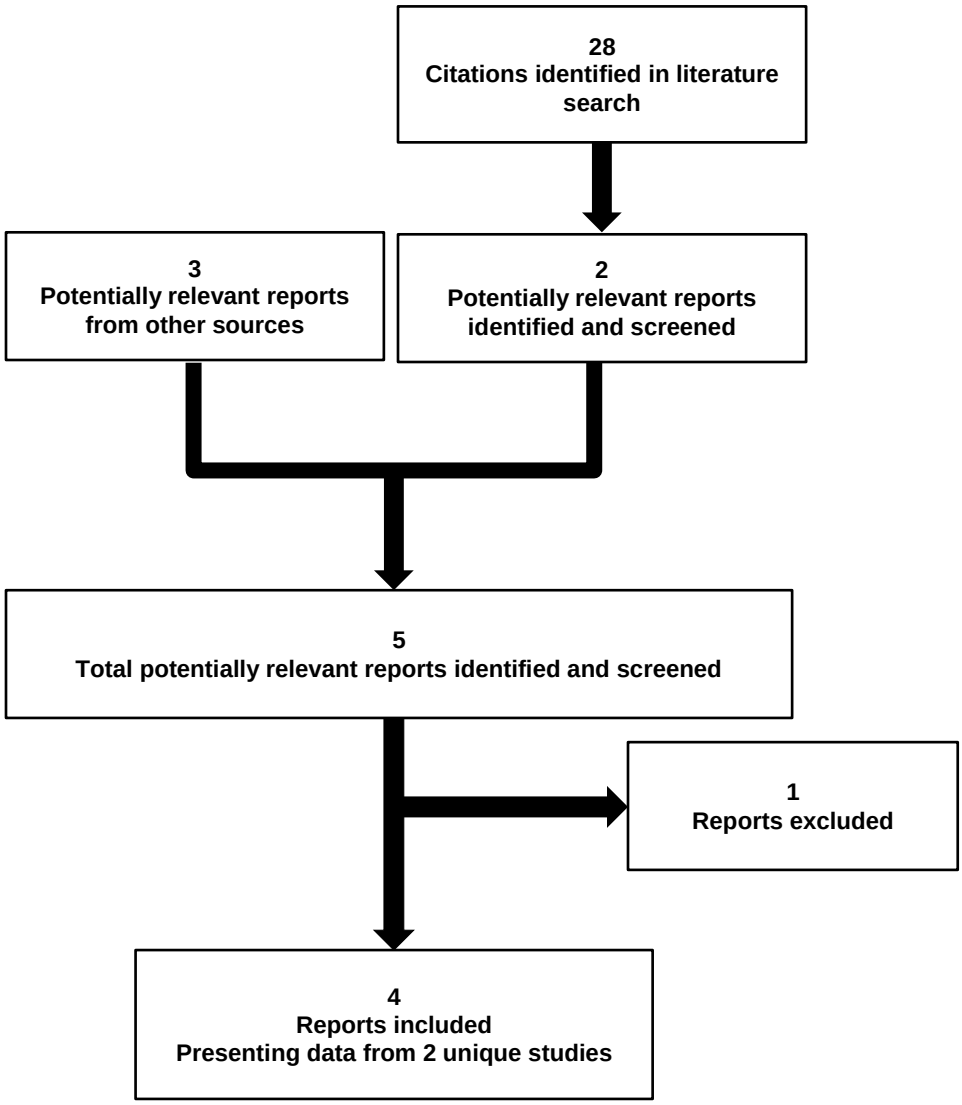

Table 5: Details of Included Studies

		POLARIS-1	POLARIS-4
Designs and Populations	**Study Design**	Phase III, randomized, placebo-controlled DB trial	Phase III, randomized, controlled open-label trial
	Locations	US, France, Canada, the UK, Germany, Australia, and New Zealand	US, Canada, New Zealand, Australia, France, Germany, and the UK
	Randomized (N)	415	333
	Inclusion Criteria	• Adults (≥ 18 years) with chronic HCV infection • Prior NS5A inhibitor treatment (minimum 4 weeks in duration) with or without cirrhosis (minimum 30% with cirrhosis) • HCV RNA ≥ 10^4 IU/mL	• Adults (≥ 18 years) with chronic HCV infection • Treatment experienced with a non-NS5A inhibitor DAA-containing regimen of at least a 4-week duration with or without cirrhosis (minimum 30% with cirrhosis) • HCV RNA ≥ 10^4 IU/mL
	Exclusion Criteria	• Clinically significant illness other than HCV • Hepatic decompensation • Solid organ transplant • Hepatitis B or HIV infection • Liver disease other than HCV • Significant cardiac disease, or an ECG with clinically significant abnormalities • Significant alcohol or drug abuse in the past year • Unstable psychiatric condition • Malignancy within the past 5 years • ALT or AST > 10 x ULN; direct bilirubin > 1.5 x ULN, albumin < 3 g/dL • Platelets < 50,000/mcL, hemoglobin < 10 g/dL, INR > 1.5 x ULN • CrCl < 50 mL/min	• Patients whose sole DAA exposure was to an NS3/4A protease inhibitor • Clinically significant illness other than HCV • Hepatic decompensation • Solid organ transplant • Hepatitis B or HIV infection • Liver disease other than HCV • Significant cardiac disease, or an ECG with clinically significant abnormalities • Significant alcohol or drug abuse in past year • Unstable psychiatric condition • Malignancy within the past 5 years • ALT or AST > 10 x ULN; direct bilirubin >1.5 x ULN, albumin < 3 g/dL • Platelets < 50,000/mcL, hemoglobin < 10 g/dL, INR > 1.5 x ULN • CrCl < 50 mL/min
Drugs	**Intervention**	Sofosbuvir 400 mg, velpatasvir 100 mg, voxilaprevir 100 mg daily for 12 weeks	Sofosbuvir 400 mg, velpatasvir 100 mg, voxilaprevir 100 mg daily for 12 weeks
	Comparator(s)	Placebo for 12 weeks	Sofosbuvir 400 mg, velpatasvir 100 mg daily for 12 weeks
Duration	**Phase**		
	Run in		
	Double blind	12 weeks	
	Open label		12 weeks
	Follow-up	4 to 24 weeks	Up to 24 weeks
Outcomes	**Primary End Point**	SVR 12 versus performance goal of 85%	SVR 12 versus performance goal of 85%
	Other End Points	• SVR4, SVR24 • % with HCV RNA < LLOQ by study visit • HCV RNA values over time • Virologic failure (on-treatment failure, relapse, or other failures) • SF-36 • CLDQ-HCV • FACIT-F • WPAI: Hepatitis C	• SVR4, SVR24 • % with HCV RNA < LLOQ by study visit • HCV RNA values over time • Virologic failure (on-treatment failure, relapse, or other failures) • SF-36 • CLDQ-HCV • FACIT-F • WPAI: Hepatitis C

		POLARIS-1	POLARIS-4
NOTES	**Publications**	Bourliere 2017[26]	Bourliere 2017[26]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CLDQ-HCV = Chronic Liver Disease Questionnaire-HCV; CrCl = creatinine clearance; DAA = direct-acting antiviral agent; DB = double blind; ECG = electrocardiogram; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HCV = hepatitis C virus; INR = International Normalized Ratio; LLOQ = lower limit of quantification; NS3/4A = nonstructural viral protein 3/4A; NS5A = nonstructural viral protein 5A; RNA = ribonucleic acid; SF-36 = 36-Item Short Form Survey Instrument; SVR 12 = sustained virologic response 12 weeks after the end of treatment; ULN = upper limit of normal; WPAI: Hepatitis C = Work Productivity and Activity Impairment Questionnaire, Hepatitis C.
Note: Two additional reports were included: CADTH Common Drug Review submission[27] and the Health Canada reviewer's report.[28]
Source: Bourliere 2017[26] and Clinical Study Reports.[6,7]

Included Studies

Description of Studies

A total of two pivotal phase III clinical trials were included in this review (POLARIS-1, and POLARIS-4). The primary outcome in both trials was sustained virologic response at 12 weeks after the end of treatment (SVR 12).

POLARIS-1 (N = 415), was a phase III, randomized, double-blind, placebo-controlled, multi-centre international study that assessed the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL/VOX treatment compared with 12 weeks of placebo treatment in DAA-experienced patients with chronic HCV infection who had previously been treated with a nonstructural protein (NS) 5A inhibitor. Patients with genotype 1 HCV infection were randomized in a 1:1 double-blind manner to receive the SOF/VEL/VOX (400/100/100 mg) tablet once daily with food for 12 weeks or an identical-looking placebo with food for 12 weeks. Randomization was stratified by presence or absence of cirrhosis. Patients with genotypes 2, 3, 4, 5, or 6 were assigned to receive 12 weeks of SOF/VEL/VOX. An interactive Web response system was used to manage randomization and assign patients to groups. POLARIS-1 had a planned enrolment of 100 genotype 1 patients per randomized group. Approximately 100 patients with genotype 3, 50 patients with genotype 4, and 30 patients with other genotypes were planned for enrolment in the SOF/VEL/VOX group regardless of cirrhosis status. Enrichment criteria were applied so at least 30% of patients enrolled with genotypes 1, 3, and 4 had cirrhosis at baseline. Patients who received placebo treatment had the option to receive open-label SOF/VEL/VOX in a deferred treatment substudy.

POLARIS-4 (N = 333) was a phase III, randomized, open-label, multi-centre international study that evaluated the safety and efficacy of SOF/VEL/VOX treatment for 12 weeks and SOF/VEL treatment for 12 weeks in DAA-experienced patients with chronic HCV infection who had not previously been treated with an NS5A inhibitor. Patients who had DAA exposure to an NS3/4A protease inhibitor only were excluded. Patients with HCV genotype 1, 2, or 3 were randomized in a 1:1 ratio to receive SOF/VEL/VOX (400/100/100 mg) once daily with food for 12 weeks or SOF/VEL 12 (400/100 mg) once daily without regard to food for 12 weeks. Randomization was stratified by HCV genotype (1, 2, or 3) and cirrhosis status (presence or absence). An interactive Web response system was used to manage enrolment, randomization, and treatment assignment. POLARIS-4 had a planned enrolment of 350 patients with HCV genotype 1, 2, or 3 (with 100 genotype 1 patients per randomized group, 25 genotype 2 patients per randomized group, and 50 genotype 3 patients per randomized group). Approximately 30 patients with other genotypes were planned for enrolment in the SOF/VEL/VOX group regardless of cirrhosis status. Enrichment criteria

were applied so at least 30% of patients enrolled with genotype 1, 2, or 3 would have cirrhosis.

Populations

Inclusion and Exclusion Criteria

In the POLARIS-1 and POLARIS-4 trials, eligible patients were males or nonpregnant/nonlactating females of ≥ 18 years of age, with HCV RNA levels ≥ 10,000 IU/mL at the time of screening, and chronic HCV infection (≥ 6 months), with or without cirrhosis. Patients included in the POLARIS-1 trial were treatment experienced with an NS5A inhibitor-containing regimen for at least four weeks. The most recent treatment was required to have been completed at least 8 weeks prior to screening, and patients could not have discontinued the most recent regimen due to an adverse event (AE) or virologic failure due to noncompliance. Patients included in the POLARIS-4 trial were treatment experienced with a non-NS5A inhibitor DAA-containing regimen for at least four weeks. The most recent treatment was required to have been completed at least 8 weeks prior to screening, and patients could not have discontinued the most recent regimen due to an AE or virologic failure due to noncompliance.

POLARIS-1 and POLARIS-4 trials excluded patients with a gastrointestinal disorder or post-operative condition that could have interfered with the absorption of the study drug, clinical hepatic decompensation (e.g., ascites, encephalopathy, or variceal hemorrhage), hepatitis B virus or HIV coinfection, malignancy, solid organ transplant, alcohol or drug abuse, chronic liver disease of a non-HCV etiology, a history of HCC, clinically significant illness (other than HCV), unstable psychiatric condition, significant cardiac disease, electrocardiogram with clinically significant abnormalities, creatinine clearance < 60 mL/min, platelets < 50,000/µL. In addition, the POLARIS-4 trial excluded patients who only had DAA exposure to an NS3/4A protease inhibitor.

Baseline Characteristics

The trials enrolled patients with a mean age per treatment group that ranged from 57 years to 59 years. Patients were predominantly white (80% to 88%) and male (76% to 80%).

In the POLARIS-1 trial, baseline characteristics were generally balanced between the SOF/VEL/VOX and placebo 12-week groups. In the SOF/VEL/VOX 12-week group, the majority of patients had genotype 1 HCV infection (57.0% [1a = 38.4%, 1b = 17.1%, and 1 other = 1.5%]) or genotype 3 HCV infection (29.7%). A greater number of patients with genotype 1 HCV infection and fewer patients with genotype 2, 3, 4, 5, and 6 and unknown HCV infection were enrolled into the SOF/VEL/VOX 12-week group than planned according to protocol specification. In the SOF/VEL/VOX 12 week group, 121 patients (46%) had cirrhosis, which was higher than the minimum target of 30% and reflects the enrichment for cirrhosis in the DAA-experienced population. In comparison, only 34% of the placebo group had cirrhosis. In the SOF/VEL/VOX group, 99.6% had been previously treated with an NS5A inhibitor, with the most common NS5A inhibitors being ledipasvir (LDV) (50.6%), daclatasvir (26.6%), and ombitasvir (11.4%). One patient (0.4%) had failed prior treatment with only an NS5B inhibitor (SOF).

In the POLARIS-4 trial, baseline characteristics were balanced across treatment groups. Most patients had genotype 1 (43.2% [1a, 29.4%; 1b, 13.8%]) or genotype 3 (31.8%) HCV infection. 19 patients with genotype 4 HCV infection were enrolled into the SOF/VEL/VOX 12-week group, which was fewer than planned according to protocol specification. No

patients with genotype 5 or 6 HCV infection were enrolled into this study. SOF/VEL had a slightly higher percentage of patients with genotype 2 and 3 infection, whereas SOF/VEL/VOX had all the patients infected with genotype 4. Overall, 46% of patients had cirrhosis, which was more than the minimum enrolment target of 30% and reflects the enrichment of cirrhosis in the DAA-experienced patient population. Most patients (73.0%) had been previously treated with an NS5B inhibitor only; 25.2% of patients had been previously treated with a combination of an NS5B inhibitor and an NS3 inhibitor. For patients with genotype 1 HCV infection, 56% had had prior exposure to SOF or SOF + SMV (simeprevir). For patients with genotype 2, 3, or 4 HCV infection, the majority of patients (95%) had prior exposure to SOF. Five DAA-experienced patients (1.5%) whose only DAA exposure was with an NS3/4A PI were enrolled (two in the SOF/VEL/VOX 12-week group and three in the SOF/VEL 12 week group). One DAA-naive patient with genotype 1a HCV infection, who had been previously treated with PR, was enrolled in the SOF/VEL 12-week group.

Table 6: Summary of Baseline Characteristics

	POLARIS-1		POLARIS-4	
Treatment Group	**SOF/VEL/VOX 12 Weeks**	**Placebo 12 Weeks**	**SOF/VEL/VOX 12 Weeks**	**SOF/VEL 12 Weeks**
Total N	**263**	**152**	**182**	**151**
Age, mean (SD)	58 (8.5)	59 (8.0)	57 (9.0)	57 (7.3)
Male, n (%)	200 (76)	121 (80)	143 (79)	114 (76)
Race, n (%)				
White	211 (80)	124 (82)	160 (88)	131 (87)
Black or African American	38 (14)	22 (15)	16 (9)	13 (9)
Asian	8 (3)	6 (4)	2 (1)	4 (3)
Other	6 (2)	0	4 (2)	3 (2)
HCV Genotype, n (%)				
Genotype 1	150 (57)	150 (99)	78 (43)	66 (44)
Genotype 2	5 (2)	0	31 (17)	33 (22)
Genotype 3	78 (30)	0	54 (30)	52 (34)
Genotype 4	22 (8)	0	19 (10)	0
Genotype 5	1 (<1%)	0	0	0
Genotype 6	6 (2)	2 (1)	0	0
Baseline HCV RNA				
Log10 IU/mL, mean (SD)	6.3 (0.68)	6.3 (0.63)	6.3 (0.56)	6.3 (0.66)
≥ 800,000 IU/mL, n (%)	190 (72)	116 (76)	136 (75)	113 (75)
Cirrhosis, n (%)	121 (46)	51 (34)	84 (46)	69 (46)
Genotype 1	51 (34.0)	NR	28 (35.9)	23 (34.8)
Genotype 1a	33 (32.7)	NR	17 (31.5)	16 (36.4)
Genotype 1b	16 (35.6)	NR	11 (45.8)	7 (31.8)
Genotype 2	0	NA	13 (41.9)	16 (48.5)
Genotype 3	56 (71.8)	NA	31 (57.4)	30 (57.7)
Genotype 4	14 (63.6)	NA	12 (63.2)	0
Genotype 5	0	NA	0	0
Genotype 6	0	NR	0	0
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	POLARIS-1		POLARIS-4	
Treatment Group	**SOF/VEL/VOX 12 Weeks**	**Placebo 12 Weeks**	**SOF/VEL/VOX 12 Weeks**	**SOF/VEL 12 Weeks**
Total N	**263**	**152**	**182**	**151**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior HCV therapy, n/N (%)				
DAA naive	NA	NA	0	1 (1)
NS5B only	NA	NA	134 (74)	109 (72)
NS5B + NS3	NA	NA	46 (25)	38 (25)
NS5A + NS5B	161 (61)	81 (53)	NA	NA
NS5A + NS3 ± NS5B	83 (32)	61 (40)	NA	NA
NS5A ± other	18 (7)	9 (6)	NA	NA
Other	1 (<1)	1 (1)	2 (1)	3 (2)
Prior treatment response, n/N (%)				
Nonresponder	20 (8)	10 (7)	7 (4)	12 (8)
Relapse	224 (85)	125 (82)	171 (94)	131 (87)
Other	19 (7)	17 (11)	4 (2)	8 (5)
Baseline eGFR (mL/min)				
Mean (SD)	119.2 (35.7)	113.1 (33.6)	123.3 (37.9)	123.8 (36.3)
Range	39.9, 229.2	54.5, 215.1	53.4, 275.7	63.6, 232.5
HIV coinfection, n (%)	excluded	excluded	excluded	excluded

DAA = direct-acting antiviral agent; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; NA = not applicable, NS3 = nonstructural viral protein 3; NS5A = nonstructural viral protein 5A; NS5B = nonstructural viral protein 5B; NR = not reported; RNA = ribonucleic acid; SD = standard deviation; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir.

Source: Clinical Study Reports.[6,7]

Interventions

In the POLARIS-1 trial, patients were randomized to receive the SOF/VEL/VOX (400/100/100 mg) tablet once daily with food for 12 weeks or an identical-looking placebo with food for 12 weeks. In the POLARIS-4 trial, patients were randomized to receive SOF/VEL/VOX (400/100/100 mg) once daily with food for 12 weeks or SOF/VEL 12 (400/100 mg) once daily without regard to food for 12 weeks. In both trials, hematologic stimulating agents and chronic use of immunosuppressant drugs (e.g., corticosteroids, azathioprine, or monoclonal antibodies) and drugs with clinically important drug-drug interactions (e.g., amiodarone) were prohibited.

The stopping criteria were similar across trials where the study drug may have been discontinued in the event of a clinical or laboratory event. There was no option for dose reduction of study drug. In the POLARIS-1 trial, only the HCV RNA results at screening and post-treatment at the week 12 and 24 visits were provided to the investigator. Independent monitoring assessed potential virologic failure and the need for confirmatory HCV RNA samples. In both trials, the following on-treatment virologic response-based treatment stopping criteria were also used for the SOF/VEL/VOX 12-week group in the POLARIS-1 trial and for the SOF/VEL/VOX or SOF/VEL 12-week groups in the POLARIS-4 trial:

- Confirmed HCV RNA ≥ lower limit of quantification (LLOQ) after two consecutive HCV RNA < LLOQ
- Confirmed > 1 log10 increase in HCV RNA from on-treatment nadir.

Confirmation was performed as soon as possible and required within two weeks after the initial observation indicating virologic failure during the on-treatment phase.

Outcomes

In both trials, the primary efficacy outcome measure was the proportion of patients achieving SVR 12, defined as an HCV RNA < the LLOQ 12 weeks after cessation of treatment. Other virologic outcomes reported included virologic failure, on-treatment virologic failure, and relapse.

In both trials, on-treatment virologic failure was defined as a breakthrough (an HCV RNA ≥ LLOQ after having previously had an HCV RNA < LLOQ while on treatment, as confirmed with two consecutive values or the last available on-treatment measurement with no subsequent follow-up values), rebound (a > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment, as confirmed with two consecutive values or the last available on-treatment measurement with no subsequent follow-up values), or nonresponse (an HCV RNA persistently ≥ LLOQ through eight weeks of treatment).

Relapse was defined as an HCV RNA ≥ LLOQ during the post-treatment period after having achieved an HCV RNA < LLOQ at the end of treatment, as confirmed with two consecutive values or the last available post-treatment measurement. The denominator for relapse was the number of patients who had had an HCV RNA < LLOQ at the last observed on-treatment measurement.

Both trials evaluated patient-reported outcomes as exploratory outcomes. The instruments used included the 36-Item Short Form Survey Instrument (SF-36), the Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and the Work Productivity and Activity Impairment Questionnaire, Hepatitis C instrument (WPAI: Hepatitis C).

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to measure health-related quality of life (HRQoL). It consists of eight domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS). All domains and summary scores are measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use, a minimal clinically important difference (MCID) of 2 to 4 points for each domain or 2 to 3 points for the MCS and PCS has been reported in the literature.[29] No MCID estimates in patients with CHC were found for the component scores. It is unclear if the MCID estimates from other conditions or the general population are generalizable to HCV.

The CLDQ-HCV, which is an HRQoL instrument for patients with chronic liver disease, has 29 items in four domains: activity/energy, emotional, worry, and systemic.[30] Each item on the CLDQ-HCV questionnaire is open ended and may be answered with one of seven response options rated on a Likert scale from 1 to 7. A score of 1 means the symptom being assessed is “present always,” while a score of 7 means the symptom is “never present.” Therefore, a higher score corresponds to a better HRQoL while a lower score corresponds to a worse HRQoL. The domain score is the sum of the item scores for that domain, divided by the number of items in that respective domain.[30] The overall CLDQ score is the mean of the domain scores.[30] An MCID for CLDQ-HCV has not been estimated.

The FACIT-F is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, and energy, as well as fatigue's impact on daily activities and function. The fatigue subscale has a seven-day recall period and includes 13 items scored using a 4-point Likert scale (with a subscale score range 0 to 52).[31] Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale (40 items in total), make up the total score, which ranges from 0 (worst) to 160 (best).[31,32] Alternatively, the Trial Outcome Index score may be calculated by summing the physical well-being, functional well-being, and fatigue subscales.[32] Although no information on the validity of FACIT-F or its MCID in hepatitis C patients was found, the MCID for the Functional Assessment of Cancer Therapy-General total score ranged from 3 to 7 points in cancer patients, and the MCID in the FACIT-F ranged from 3 to 4 points in rheumatoid arthritis patients.[32,33]

The WPAI: Hepatitis C is an instrument used to measure the impact of a disease on work and on daily activities. It elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing of work was challenging, and the extent to which the patient was limited at work (i.e., experienced work impairment) during the past seven days. The activity impairment domain refers to the impairment in daily activities other than work. The scores are presented as a percentage, with lower values indicating a better quality of life. There is no known MCID or validity data in patients with hepatitis C. An MCID of 7% has been reported for patients with Crohn's disease.[34]

An AE was any untoward medical event in a patient who had received a study drug that may or may not have had a causal relationship with treatment. A serious AE (SAE) was defined as any event that resulted in death, a life-threatening situation, a persistent or significant disability, or a congenital anomaly; required hospitalization or prolongation of hospitalization; or may have required medical intervention to prevent one of these outcomes. Treatment-emergent events were those with an onset on or after the start of study drug up to 30 days after permanent discontinuation of drug, or those that led to permanent discontinuation of the study drug.

Statistical Analysis

In the POLARIS-1 trial, a sample size of 280 patients in the SOF/VEL/VOX 12-week group was planned to provide > 90% power to detect an improvement in SVR 12 from the performance goal of 85% using a two-sided exact one-sample binomial test at the 0.05 significance level. The two-sided 95% exact confidence interval (CI) for SVR 12 was based on the Clopper-Pearson method. The performance goal of 85% was chosen because it was difficult to characterize a historical control rate for all HCV genotypes included in this study, given the lack of a standard of care across genotypes. Given these difficulties, rather than use a historical control rate as the basis for assessing the primary end point, a performance goal was defined as a benchmark against which the efficacy of SOF/VEL/VOX was tested; therefore, a high benchmark of 85% was set. A number of subgroup analyses were conducted for SVR 12, including the following that were listed in the review protocol: HCV genotype, presence of cirrhosis, prior HCV treatment experience, and HCV RNA levels. No multiplicity adjustment was made for testing (only one test was performed).

In the POLARIS-4 trial, sample sizes of 205 patients in the SOF/VEL/VOX 12-week group and 175 patients in the SOF/VEL 12-week group were planned to provide > 90% power to detect an improvement in SVR 12 rate from the performance goal of 85% using a two-sided exact one-sample binomial test at the 0.025 significance level. The two-sided 95% exact CI for SVR 12 was based on the Clopper-Pearson method. The performance goal of 85% was chosen for the same reasons provided for the POLARIS-1 trial. A number of subgroup

analyses were conducted for SVR 12, including the following that were listed in the review protocol: HCV genotype, presence of cirrhosis, prior HCV treatment experience, and HCV RNA levels. The POLARIS-4 trial had two primary efficacy tests. The SVR 12 rate in the SOF/VEL/VOX 12-week group was compared with the performance goal of 85%, and the SVR 12 rate in the SOF/VEL 12-week group was compared with the performance goal of 85%. To control the overall type I error, each primary efficacy test was tested at the significance level of 0.025 using a Bonferroni adjustment.

In both trials, missing HCV RNA data were imputed as follows:

- If the values were "< LLOQ target not detected" for the time point preceding and following the missing data point, the value was imputed as "< LLOQ target not detected".
- If the values were "< LLOQ detected" for the time point preceding and following the missing data point, or a combination of "< LLOQ detected" or "not detected" before or after, the value was imputed as "< LLOQ detected".
- If HCV RNA results were not available within the window set by imputation rules, then the data were imputed as ≥ LLOQ detected.

In the POLARIS-1 trial, the exploratory efficacy end points for SF-36 (all domains and component scores), CLDQ-HCV (overall score), FACIT-F (trial outcome index and total score), and WPAI: Hepatitis C (percentage of overall work impairment for patients who worked in the past week and percentage of activity impairment for all patients) were reported at baseline, week four, week 12, the end of treatment, post-treatment week four (all groups), and post-treatment weeks 12 and 24 (SOF/VEL/VOX treatment group only). There was no imputation of missing patient-reported outcome data up to and including the post-treatment week 12 visit in the SOF/VEL/VOX group and up to the four-week post-treatment visit in the placebo group. In the POLARIS-4 trial, the exploratory efficacy end points for SF-36 (all domains and component scores), CLDQ-HCV (overall score), FACIT-F (trial outcome index and total score) and WPAI: Hepatitis C (percentage of overall work impairment for patients who worked in the past week and percentage of activity impairment for all patients) were reported at baseline, week four, week 12, the end of treatment, and post-treatment weeks four, 12, and 24 for both treatment groups. There was no imputation of missing patient-reported outcome data up to and including the post-treatment week 12 visit in both treatment groups. In both trials, a Wilcoxon signed rank test was used to explore within-group change from baseline values, and a Wilcoxon rank sum test was used for between-group changes from baseline analyses. Though inferential statistics (*P* values) were presented, the results should be interpreted with caution, as multiple endpoints were being tested, and the study was not powered to test these exploratory endpoints.

Analysis Populations

In both trials, the primary efficacy analysis population was the full analysis set (FAS), which included all patients randomized or enrolled into the study who received at least one dose of study drug. Patients were grouped according to the assigned treatment.

In both trials, the safety set included all enrolled patients who received at least one dose of study drug, analyzed according to the treatment actually received.

Patient Disposition

Of the 520 patients screened for POLARIS-1, 104 (20%) were not enrolled. Of the 104 patients who failed screening, four patients met the eligibility criteria but did not enroll due to withdrawal of consent. Of the 99 patients who did not meet eligibility criteria, the most

common reasons were that the patient had lab values that were outside the range (48%), the patient did not have HCV RNA values ≥ 10^4 IU/mL (14%), or liver imaging had not been performed within past six months (14%).

Of the 397 patients screened for POLARIS-4, 64 (16%) were not enrolled. Of the 64 patients who failed screening, four patients met the eligibility criteria but did not enroll because they were lost to follow-up or withdrew consent (two patients each). Of the 60 patients who did not meet eligibility criteria, the most common reasons were that the patient had lab values that were outside the range (50%), the patient had a history of clinically significant illness or any other major medical disorder (22%), the patient was treatment experienced with a non-NS5A inhibitor-containing regimen (excluding NS3/4A alone) (15%), or the patient did not have HCV RNA values ≥ 10^4 IU/mL (10%).

Discontinuation rates were low in both trials, with the proportion of patients who discontinued study medication ranging from 0% to 2.0%. The highest discontinuation rate was in the POLARIS-1 trial in the placebo for the 12-week treatment group (Table 7).

Table 7: Patient Disposition

	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX 12 Weeks	**Placebo 12 Weeks**	**SOF/VEL/VOX 12 Weeks**	**SOF/VEL 12 Weeks**
Screened, N	520		397	
Randomized, N (%)	416 (80)		333 (84)	
	264	152	182	151
Randomized and treated, N (%)	263	152	182	151
Completed treatment, N (%)	261	149	182	149
Discontinued drug, N (%)	2 (0.8)	3 (2.0)	0	2 (1.3)
Adverse events	1 (0.4)	3 (2.0)	0	1 (0.7)
Lost to follow-up	1 (0.4)	0	0	0
Lack of efficacy	0	0	0	1 (0.7)
Discontinued study, N (%)	3 (1.1)	1 (0.7)	5 (2.7)	2 (1.3)
Lost to follow-up	1 (0.4)	NR	2 (1.1)	1 (0.7)
Death	0	0	2 (1.1)	0
Withdrew consent	2 (0.8)	NR	0	1 (0.7)
Protocol violation		NR	1 (0.5)	0
FAS, N	263	152	182	151
Safety, N	263	152	182	151

FAS = full analysis set; NR = not reported; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir.

Source: Clinical Study Reports.[6,7]

Exposure to Study Treatments

In the POLARIS-1 trial, the majority of patients in each treatment group (98.0% in the placebo group and 99.2% in the SOF/VEL/VOX group) completed their assigned treatment duration. The median treatment duration was 12 weeks (ranging from 0.3 to 12.3) in the placebo group and 12.0 weeks (ranging from 1.7 to 12.6) in the SOF/VEL/VOX group.

In the POLARIS-4 trial, most patients received 12 weeks of assigned treatment in the SOF/VEL/VOX and SOF/VEL groups (100% and 98.7%, respectively). The median treatment duration was 12 weeks (ranging from 8.0 to 12.4) in the SOF/VEL group and 12.0 weeks (ranging from 11.7 to 12.4) in the SOF/VEL/VOX group.

Critical Appraisal

Internal Validity

In the POLARIS-1 trial, only patients with genotype 1 HCV infection were randomized to receive SOF/VEL/VOX or placebo, while patients with genotype 2, 3, 4, 5, or 6 HCV infection were assigned to the SOF/VEL/VOX treatment group only. In the POLARIS-4 trial, patients with genotype 4 HCV infection were assigned to the SOF/VEL/VOX treatment group only, while patients with HCV genotype 1, 2, or 3 HCV infection were randomized in a 1:1 ratio into the SOF/VEL/VOX or SOF/VEL groups. In both trials, for the patients who were randomized, the method of randomization was sufficiently reported and deemed appropriate (interactive Web response system) and the patient characteristics appeared to have been similar between groups. POLARIS-4 was an open-label trial; while SVR 12 is an objective measure and may not be largely affected by an open-label design, awareness of treatment allocation might have influenced subjective measures such as HRQoL and reporting of AEs and contributed to patient decisions to continue/discontinue treatment and/or adherence. However, it does not seem that awareness of treatment allocation affected such measures in the trials. In the POLARIS-1 trial, all patients with HCV genotype 2, 3, 4, 5, or 6 were enrolled in the SOF/VEL/VOX 12-week treatment group; as a result, these patients might have been aware of treatment allocation, which might have influenced subjective measures such as HRQoL measures and reporting of AEs, although globally, the prevalence of these viral variants in most regions is very small, which likely limited the ability to randomly assign them.

In both trials, imputation and the handling methods used for the missing data for the SVR seemed appropriate.

Both trials compared treatment versus a performance goal of 85%. However, it is unclear how the performance goal was chosen. Also, POLARIS-4 did not compare between treatment arms, even though it had an active treatment comparator (SOF/VEL). Currently, there is another treatment (GP) that is indicated for the treatment of adult patients with HCV genotype 1 infection who were previously treated with a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor (but not both classes of inhibitors); however, none of the trials compared directly with GP or used it as a historical control. It is acknowledged, however, that GP is a new product that was not available during the design and conduct of the POLARIS-1 and POLARIS-4 trials. Despite the limitations associated with the design of the POLARIS-1 and POLARIS-4 trials, the draft guidance document produced by the FDA noted that DAA treatment-experienced patients constitute an emerging population in need of effective HCV therapies, and detailed guidance for phase III trial design cannot be provided due to the limited available efficacy data in this population.[35]

[redacted]

[redacted] Therefore, it is not possible to judge if the difference between treatment groups is clinically meaningful. Finally, MCIDs specific to CHC PROs are unknown, which also limits the ability to interpret these results.

The intention-to-treat (ITT) population was not used in the analyses; the FAS population, which consisted of patients who were randomized into the study and received at least one dose of study drug, was used instead. This FAS population is a modified ITT population. Although the analysis was therefore by definition not a true ITT analysis, there were few (e.g., one patient) or no differences in the numbers of patients in the randomized and FAS populations in both trials.

External Validity

The generalizability of trial results may be limited for more complex patients, as important concurrent conditions were listed as exclusion criteria in the trials. For example, patients with HIV coinfection were excluded from both trials. No patients who had undergone a transplant were included in the trials. Both trials excluded patients with severe renal impairment or ESRD. Few patients with genotype 5 and 6 HCV infection were enrolled in the POLARIS-1 trial, although globally, the prevalence of these viral variants in most regions is low.[36] In total, 80 of the patients enrolled were Canadian (10.1% in the POLARIS-1 trial, and 11.4% in the POLARIS-4 trial).

Comparative data are lacking, as the POLARIS-1 trial did not include another DAA-based regimen as a control group. Thus, it is difficult to determine the treatment's comparative effectiveness and place in therapy relative to other regimens currently approved in Canada, in particular versus GP for patients with genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor. It is acknowledged, however, that GP is a new product and it was not available during the design and conduct of the POLARIS-1 and POLARIS-4 trials. In both trials, the treatment duration was sufficient to determine virologic response but not to assess longer-term morbidity, mortality, and safety.

Considerable proportions of patients (16% to 20%) were screened for enrolment but did not enter the treatment phase of the trials. The most common reason stated was that patient lab values were outside the range established for inclusion. Both trials excluded patients with hepatitis B coinfection, malignancy, and recent alcohol or drug abuse; therefore, the generalizability of the results of the included studies to these populations is unknown. No data were available on other subgroups of interest, such as patients with liver transplantation or renal insufficiency.

In the POLARIS-1 trial, patients with genotype 2, 3, 4, 5, or 6 were assigned to the SOF/VEL/VOX treatment group only, and in the POLARIS-4 trial, patients with genotype 4 were assigned to SOF/VEL/VOX treatment group only. This uneven distribution of patients

with HCV genotype 2, 3, 4, 5, or 6 infection in the POLARIS-1 trial and with HCV genotype 4 infection in the POLARIS-4 trial limits the generalizability of the results for these particular populations.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 4). See Appendix 4 for detailed efficacy data. Hepatic-related morbidity was an outcome of interest; however, the trials were not designed to assess the impact of treatment on longer-term hepatic disease.

Virologic Response

In the POLARIS-1 trial, which included patients with genotypes 1, 2, 3, 4, 5, or 6 chronic HCV infection who have previously been treated with a DAA regimen containing an NS5A inhibitor, the SOF/VEL/VOX 12-week treatment group met the primary end point of an SVR 12 rate that was statistically superior relative to the pre-specified performance goal of 85% ($P < 0.001$). In the SOF/VEL/VOX 12-week treatment group, 96.2% (95% CI, 93.1% to 98.2%) of patients achieved SVR 12 (Table 8).

In the POLARIS-1 trial, a total of 10 of 263 patients (3.8%) in the SOF/VEL/VOX 12-week treatment group did not achieve SVR 12. Of these, one patient had on-treatment virologic failure (breakthrough), and six patients relapsed. Of the patients who had relapsed, one patient had genotype 1a HCV infection and cirrhosis and was found to be nonadherent to the study drug, and three patients with genotype 3 HCV infection and cirrhosis had relapsed at the post-treatment week 4 visit. Three patients (one patient was cirrhotic with HCV genotype 4, one patient was cirrhotic with genotype 1a, and one patient had genotype 3 HCV infection and cirrhosis) achieved SVR4 but had relapse determined at the post-treatment week 12 visit. Three additional patients did not achieve SVR 12 and did not meet virologic failure criteria; one of whom had genotype 4 HCV infection and cirrhosis discontinued treatment with SOF/VEL/VOX on day 12 due to a grade 3 angioedema attributed to a newly initiated concomitant medication (ramipril) and then withdrew consent for further follow-up. Another patient had genotype 1a HCV infection and no cirrhosis; this patient had no HCV RNA detected at weeks 2, 4, and 8 but was lost to follow-up at the post-treatment week 4 visit. Another patient had genotype 1a HCV infection and no cirrhosis; this patient completed 12 weeks of treatment with SOF/VEL/VOX and achieved SVR4 but withdrew consent before the post-treatment week 12 visit.

In the POLARIS-1 trial, high SVR 12 rates were achieved in all subgroups. SVR 12 rates were lower in patients with HCV genotype 4 infection (90.9% [95% CI, 70.8% to 98.9%]). Notably, the number of patients in this subgroup was small, and a single patient who withdrew consent contributed to the lower SVR 12 rates for this group. For patients with genotype 1 HCV infection, the SVR 12 rate was 97.3% (95% CI, 93.3% to 99.3%). Patients with genotype 3 and 4 infection had SVR 12 rates of 94.9% (95% CI, 87.4% to 98.6%) and 90.9% (95% CI, 70.8% to 98.9), respectively. For the fewer patients with unknown or the less common HCV genotypes 2, 5, and 6, SVR 12 rates were 100% for all groups. The SVR 12 rate was lower for patients with cirrhosis (93.4%, [95% CI, 87.4% to 97.1%]) compared with patients without cirrhosis (98.6%, [95% CI, 95.0% to 99.8%]). The SVR 12 rate was 92.9% (95% CI, 82.7% to 98.0%) in patients with genotype 3 HCV infection and cirrhosis. The SVR 12 rates by prior HCV treatment regimens were high regardless of prior DAA-class combinations (NS5A + NS5B inhibitor: 93.8% [95% CI, 88.9% to 97.0%], NS5A + NS3

inhibitor ± NS5B inhibitor: 100.0% [95% CI, 95.7% to 100.0%]) or specific DAA combinations ([redacted]) (Table 11). No patient in the 12-week placebo group (0 of 152) achieved SVR 12.

In the POLARIS-4 trial, which included DAA-experienced patients with genotype 1, 2, 3, or 4 chronic HCV infection who have not received an NS5A inhibitor, the SOF/VEL/VOX for 12 weeks treatment group met the primary efficacy end point with a statistically significantly higher SVR 12 rate of 97.8% (95% CI, 94.5% to 99.4%) compared with the performance goal of 85% ($P < 0.001$). The SOF/VEL 12-week treatment group did not meet the primary efficacy end point with an SVR 12 rate of 90.1% (136 of 151 patients) (95% CI, 84.1% to 94.3%) compared with the performance goal of 85% ($P = 0.092$) (Table 8).

In the POLARIS-4 trial, in the SOF/VEL/VOX 12-week treatment group, four of 182 patients (2.7%) did not achieve SVR 12. Of these, one patient relapsed and three patients were categorized as “Other.” Patients were categorized as “Other” if they did not achieve SVR 12 and did not meet criteria for virologic failure. Of the patients who were categorized as “Other,” one patient had genotype 1b HCV infection and died of illicit drug overdose two days after the last dose of study drug; this patient had no detected HCV RNA at the week 8 visit, the last visit prior to death. The two other patients categorized as “Other,” who had genotype 3a HCV infection, did not have a post-treatment week 12 assessment, and they had no detected HCV RNA at the last available HCV RNA assessment at week 8. In the SOF/VEL 12-week group, 15 of 151 patients (9.9%) did not achieve SVR 12: one patient had on-treatment virologic failure and 14 patients relapsed. The one patient who had on-treatment virologic failure during SOF/VEL treatment had genotype 2 HCV infection without cirrhosis and had breakthrough determined at the week 8 visit. This patient was discontinued from study treatment due to a lack of efficacy and did not complete study treatment. Of the 14 patients who relapsed following SOF/VEL treatment for 12 weeks, eight patients had genotype 3 HCV infection, and seven of these patients also had cirrhosis. Six patients who relapsed had genotype 1 HCV infection (three patients with genotype 1a with cirrhosis, two patients with genotype 1a without cirrhosis, and one patient with genotype 1b without cirrhosis who completed only 56 days of study treatment and discontinued treatment due to the AE of headache).

In the POLARIS-4 trial, the SVR 12 rates in the SOF/VEL/VOX 12-week treatment group were > 95.0% across subgroups of interest, including patients with cirrhosis (97.6%, [95% CI, 91.7% to 99.7%]), patients with genotype 3 infection (96.3%, [87.3% to 99.5%]), and patients with prior DAA exposure to SOF (97.7%, [95% CI, 93.5% to 99.5%]) or SOF + SMV ([redacted]%, [95% CI, [redacted]% to [redacted]%]). Only one patient in the SOF/VEL/VOX 12-week group relapsed, precluding a meaningful analysis of SVR 12 by subgroups. For patients with genotype 1 HCV infection in the SOF/VEL 12-week group, the SVR 12 rate was 90.9% (95% CI, 81.3% to 96.6%); SVR 12 rates were lower for patients with genotype 1a HCV infection (88.6%, [95% CI, 75.4% to 96.2%]) compared with genotype 1b HCV infection (95.5%, [95% CI, 77.2% to 99.9%]). Patients with genotype 2 or 3 HCV infection had SVR 12 rates of 97.0% (95% CI, 84.2% to 99.9%) and 84.6% (95% CI, 71.9% to 93.1%), respectively. For patients with cirrhosis, the SVR 12 rate in the SOF/VEL 12-week group was lower (85.5%, [95% CI, 75.0% to 92.8%]) compared with patients without cirrhosis (93.9%, [95% CI, 86.3% to 98.0%]) (Table 11). Seven of the 13 patients that did not achieve SVR 12 had genotype 3 HCV infection and cirrhosis; the SVR 12 rate in this subgroup was 76.7% (95% CI, 57.7% to 90.1%). For patients in the SOF/VEL/VOX 12-week group, 96.8% of patients (95% CI, 83.3% to 99.9%) with genotype 3 HCV infection and cirrhosis achieved SVR 12.

Table 8: Virologic Response

	POLARIS-1[a]	POLARIS-4	
	SOF/VEL/VOX 12 weeks	SOF/VEL/VOX 12 weeks	SOF/VEL 12 weeks
	N = 263	N = 182	N = 151
SVR 12 n/N (%) [95% CI]	253/263 (96.2) [93.1, 98.2]	178/182 (97.8) [94.5, 99.4]	136/151 (90.1) [84.1, 94.3]
P value (compared with performance goal of 85%)	0.001	0.001	0.092
Reason for nonresponse			
Overall virologic failure, N (%)	7 (2.7)	1 (0.5)	15 (9.9)
On-treatment virologic failure	1 (0.4)	0	1/151 (0.7)
Relapse	6/261 (2.3)	1/182 (0.5)	14/150 (9.3)
Other	3 (1.1)	3/182 (1.6)	0
Discontinued study drug prematurely	1 (0.4)	0	0
Lost to follow-up	1 (0.4)	2 (1.1)	0
Withdrew consent	1 (0.4)	0	0
Death	0	1 (0.5)	0

CI = confidence interval; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir; SVR 12 = sustained virologic response 12 weeks after the end of treatment.
[a] The placebo group was not presented because zero patients achieved virologic response.
Source: Clinical Study Reports.[6,7]

SVR 12 rates according to the presence of resistance variants at baseline were reported for both trials. In both trials, the resistance analysis population was defined as all patients in the safety analysis set with a virologic outcome.

In the POLARIS-1 trial, the resistance analysis population included 260 patients randomized/enrolled into SOF/VEL/VOX 12-week group. Table 9 presents SVR 12 rates by baseline resistance-associated variants (RAVs) (15% assay cut-off) for patients in the SOF/VEL/VOX 12-week group. In the POLARIS-1 trial, the presence of baseline RAVs did not affect the SVR 12 rate in the SOF/VEL/VOX 12-week group overall or when assessed by each genotype. Overall, the SVR 12 rate was 97.1% for patients with RAVs, and the SVR 12 rate was 97.7% for patients without RAVs. Of the 32 patients with genotype 3 and NS5A sequence available who had Y93H at baseline, 94% achieved SVR 12. Of the seven patients with virologic failure, only one patient developed treatment-emergent RAVs L31M and Y93H; this patient, who had genotype 1a, experienced virologic breakthrough at the end of treatment and had pharmacokinetic data consistent with nonadherence. No NS3, NS5A, or NS5B RAVs emerged in any of the six patients who relapsed with data available.

In the POLARIS-4 trial, the resistance analysis population included 329 patients (179 randomized/enrolled into SOF/VEL/VOX 12-week group and 151 randomized/enrolled into SOF/VEL 12-week group). Table 9 presents SVR 12 rates by baseline RAVs (15% assay cut-off) for patients in each treatment group. The presence of baseline NS3 and/or NS5A RAVs did not impact the SVR 12 rate of the SOF/VEL/VOX 12-week or the SOF/VEL 12-week groups. In the SOF/VEL/VOX 12-week group, the SVR 12 rates were 100.0% and 98.8% in patients with and without baseline NS3 and/or NS5A RAVs, respectively. In the SOF/VEL 12-week group, the SVR 12 rates were 90.0% and 89.3% in patients with and without baseline NS3 and/or NS5A RAVs, respectively. All of the four patients with genotype 3 HCV infection who had Y93H at baseline (two patients in the SOF/VEL/VOX 12-week group and two patients in the SOF/VEL 12 week group) achieved SVR 12.

Table 9: SVR 12 in Patients with Baseline NS5A or NS3 Resistance Variants (15% Cut-off)

	POLARIS-1	POLARIS-4	
	SOF/VEL/VOX 12 Weeks	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks
SVR12			
Total N	260[a]	179[b]	151
NS3 variant, n/N (%)	9/9 (100)	39/39 (100.0)	29/32 (90.6)
NS5A variant, n/N (%)	120/124 (96.8)	40/40 (100.0)	32/34 (94.1)
NS3 and NS5A variants	70/72 (97.2)	4/4 (100.0)	2/4 (50.0)
NS3 or NS5A variant, n/N (%)	199/205 (97.1)	83/83 (100.0)	63/70 (90.0)
No NS3 or NS5A RAVs	42/43 (97.7)	85/86 (98.8)	67/75 (89.3)

NS3 = nonstructural viral protein 3; NS5A = nonstructural viral protein 5A; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir; SVR 12 = sustained virologic response 12 weeks after the end of treatment.
[a] Included all patients in the safety analysis set with a confirmed virologic outcome. Three patients who failed treatment due to other non-virologic related reasons (stopped treatment, lost to follow-up, or withdrawal of consent) were excluded from this analysis.
[b] Excluding patients with a virologic outcome of "other."
Source: Clinical Study Reports.[6,7]

Health-Related Quality of Life

Both trials reported HRQoL using the SF-36 (version 2) instrument and reported data for the individual domains, as well as the MCS and PCS. Both trials also reported HRQoL using the CLDQ-HCV. For this report, the MCS and PCS of the SF-36 and the CLDQ-HCV have been summarized in Appendix 4, Table 12. HRQoL was an exploratory outcome, and there were no multiplicity adjustments applied in either study. The *P* values for the between-treatment group comparisons were based on a Wilcoxon rank sum test, which is a non-parametric statistical test, and differences in between treatment groups with the corresponding 95% CI for the treatment difference were not estimated. Results were available for ≥ 95% of patients for the SF-36 and the CLDQ-HCV. In general use, two to three points for the SF-36 MCS and PCS represent a meaningful change.[29] An MCID for CLDQ-HCV has not been estimated.

At baseline, the mean SF-36 PCS score ranged from 48 to 49.6 across treatment groups, and the scores were similar between SOF/VEL/VOX and placebo (in the POLARIS-1 trial) or SOF/VEL (in the POLARIS-4 trial). The mean within-group change from baseline ranged from 0.3 to 0.6 points at the final treatment visit, and from 0.9 to 1.5 points at the 12-week follow-up visit. No statistically significant differences were detected between SOF/VEL/VOX and placebo at the final treatment visit (the difference was not reported at the 12-week follow-up visit) or between SOF/VEL/VOX and SOF/VEL at the final treatment visit or at the 12-week follow-up visit (Appendix 4, Table 12). The results were similar for the SF-36 MCS (mean baseline: 47.8 to 49.9; mean change from baseline to end of treatment: -1.2 to 1; mean change from baseline to 12-week follow-up: 1.9 to 2.6), with no statistically significant differences detected between SOF/VEL/VOX and placebo at the final treatment visit (the difference was not reported at the 12-week follow-up visit) or between SOF/VEL/VOX and SOF/VEL at the final treatment visit or at the 12-week follow-up visit (Appendix 4, Table 12).

At baseline, the mean overall score for the CLDQ-HCV ranged from 5.1 to 5.3 across treatment groups, and scores were similar between SOF/VEL/VOX and placebo (in the POLARIS-1 trial) or SOF/VEL (in the POLARIS-4 trial). The mean within-group change from baseline ranged from 0 to 0.3 points at the final treatment visit, and from 0.4 to 0.5 points at the 12-week follow-up visit. No statistically significant difference was detected between

SOF/VEL/VOX and placebo at the final treatment visit (the difference was not reported at the 12-week follow-up visit) indicating improvement in the SOF/VEL/VOX treatment group when compared with placebo. No statistically significant difference was detected between SOF/VEL/VOX and SOF/VEL at the final treatment visit or at the 12-week follow-up visit (Appendix 4, Table 12).

Other Patient-Reported Outcomes

Both trials reported data for the FACIT-F and the WPAI: Hepatitis C (Appendix 4, Table 13). For the FACIT-F, total score data were available for ≥ 91% of patients. The WPAI overall work impairment score was reported for 44% to 57% of patients enrolled, and the activity impairment score was reported for 88% to 97% of patients. Patient-reported outcomes were exploratory in both studies, and there were no multiplicity adjustments applied in either study. The *P* values for the between treatment group comparisons were based on a Wilcoxon rank sum test, which is a non-parametric statistical test, and differences in between treatment groups with the corresponding 95% CI for the treatment difference were not estimated. The MCID in patients with hepatitis C is not known for either instrument.

The mean total FACIT-F score ranged from 116.2 to 121.4 points at baseline and changed –0.6 to 3.7 points at the final treatment visit and 6.3 to 8.2 points at the 12-week follow-up visit across treatment groups. No statistically significant differences were detected between SOF/VEL/VOX and placebo at the final treatment visit (the difference was not reported at the 12-week follow-up visit) or between SOF/VEL/VOX and SOF/VEL at the final treatment visit or at the 12-week follow-up visit (Appendix 4, Table 13).

At baseline, the mean overall work impairment score for the WPAI: Hepatitis C instrument ranged from 11.9 to 18.8. The change from baseline ranged from –3.3 to 2.7 at the final treatment visit and from -7.2 to 0 at the 12-week follow-up visit across treatment groups. The mean baseline WPAI: Hepatitis C activity impairment score ranged from 18.3 to 23.2. The change from baseline to the final treatment visit ranged from –3.5 to –1.0, and the change from baseline to the 12-week follow-up visit ranged from –8.9 to –5.4. No statistically significant differences were detected between SOF/VEL/VOX and placebo at the final treatment visit (the difference was not reported at the 12-week follow-up visit) or between SOF/VEL/VOX and SOF/VEL at the final treatment visit or at the 12-week follow-up visit for the WPAI overall work impairment or activity impairment scores (Appendix 4, Table 13).

Mortality

No deaths were reported in the POLARIS-1 trial.

Two deaths were reported among SOF/VEL/VOX-treated patients in the POLARIS-4 trial. One grade 4 AE that was reported in a patient in the SOF/VEL/VOX 12-week group, an illicit drug overdose, was further specified to be combined heroin and fentanyl toxicity; the AE occurred two days after treatment was completed, was considered serious, was not related to the study drug, and led to death. One additional nontreatment-emergent grade 4 AE, cerebral hemorrhage, was reported in a patient in the SOF/VEL/VOX 12-week group; the AE occurred [redacted] after treatment was completed, was considered serious, was not related to the study drug, and led to death. No deaths were reported among SOF/VEL-treated patients.

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Table 10 for detailed harms data.

Adverse Events

The percentage of patients who reported AEs while on SOF/VEL/VOX for 12 weeks ranged from 76.9% to 78%. 73.5% of patients who received SOF/VEL and 70% of patients who received placebo reported AEs, respectively (Table 10).

In the POLARIS-1 trial, the three most commonly reported AEs in patients who received SOF/VEL/VOX or placebo for 12 weeks were headache (66 patients [25.1%] in the SOF/VEL/VOX group and 26 patients [17.1%] in the placebo group), fatigue (56 patients [21.3%] in the SOF/VEL/VOX group and 30 patients [19.7%] in the placebo group), and diarrhea (47 patients [17.9%] in the SOF/VEL/VOX group and 19 patients [12.5%] in the placebo group), with a higher percentage of patients reporting these AEs in the SOF/VEL/VOX 12-week group than the placebo 12-week group. In the POLARIS-4 trial, the type and incidence of common AEs were similar for the two treatment groups, with the exception of diarrhea, which was reported for more patients in the SOF/VEL/VOX 12-week group compared with the SOF/VEL 12-week group (19.8% versus 4.6%). The three most commonly reported AEs in patients who received SOF/VEL/VOX for 12 weeks were headache (50 patients [27.5%]), fatigue (43 patients [23.6%]), and diarrhea (36 patients [19.8%]), while for those who received SOF/VEL for 12 weeks, they were headache (43 patients [28.5%]), fatigue (43 patients [28.5%]), and nausea (12 patients [7.9%]).

Serious Adverse Events

The percentages of patients who had serious AEs (SAEs) while on SOF/VEL/VOX for 12 weeks were 1.9% and 2.2%, respectively, in the POLARIS-1 and the POLARIS-4 trials, 2.6% among those who received SOF/VEL, and 4.6% among those who received the placebo (Table 10).

In the POLARIS-1 trial, no SAE was reported for more than one patient. All SAEs were assessed as unrelated to the study drug; one nontreatment-emergent SAE of HCC was recorded as related to the study drug at the time of database finalization, but this SAE was subsequently verified by the investigator as unrelated to the study drug. In the SOF/VEL/VOX 12-week group, no patients had SAEs that led to discontinuation or interruption of study drug. In the placebo 12-week group, one patient had an SAE (schizophrenia) that led to discontinuation of the study drug on day 57, and one patient had an SAE (atrial fibrillation) that led to an interruption of dosage.

In the POLARIS-4 trial, no SAE was reported for more than one patient. All of the SAEs were considered unrelated to the study drug and resolved. One patient in the SOF/VEL/VOX 12-week group experienced an SAE of overdose that resulted in death. Another patient in the SOF/VEL/VOX 12-week group experienced an SAE of congestive heart failure that led to interruption of the study drug.

Withdrawals Due to Adverse Events

Few patients (0% to 2.0%) stopped treatment due to AEs in all treatment groups. Withdrawals were highest in the POLARIS-1 trial in patients who received placebo for 12 weeks (2.0%) (Table 10).

Notable Harms

In the POLARIS-1 trial, one patient in each treatment group had anemia, and six patients in the SOF/VEL/VOX 12-week group (2%) and two patients in the placebo group (1%) had pruritus. In the SOF/VEL/VOX 12-week group, no patients had grade 3 or 4 elevated alanine aminotransferase (ALT) compared with three patients with grade 3 or 4 ALT elevations in the placebo 12-week group. A grade 3 increase in total bilirubin was reported in one patient in the SOF/VEL/VOX 12-week group. One nontreatment-emergent SAE of HCC was recorded as related to the SOF/VEL/VOX 12-week group at the time of database finalization but was subsequently verified by the investigator as unrelated to the study drug. There was no evidence of VOX-related hepatotoxicity.

In the POLARIS-4 trial, one patient in the SOF/VEL 12-week group had anemia, and six patients in the SOF/VEL 12-week group (4%) had pruritus. No patients in the SOF/VEL/VOX 12-week group had anemia or pruritus. Only one grade 3 chemistry laboratory abnormality of increased ALT was observed in a patient in the SOF/VEL/VOX 12-week group. This patient also had baseline grade 3 increased total bilirubin and increased aspartate aminotransferase, and all of these abnormalities were likely explained by ongoing heavy alcohol use, per the investigator. No other grade 3 or 4 chemistry laboratory abnormalities of increased ALT or total bilirubin were observed in this study. There was no evidence of VOX-related hepatotoxicity.

Table 10: Harms

	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX 12 Weeks	**Placebo 12 Weeks**	**SOF/VEL/VOX 12 Weeks**	**SOF/VEL 12 Weeks**
AEs	**N = 263**	**N = 152**	**N = 182**	**N = 151**
Patients with ≥1 AEs, n (%)	206 (78)	107 (70)	140 (76.9)	111 (73.5)
Most common AEs[a]				
Headache	66 (25)	26 (17)	50 (27.5)	43 (28.5)
Fatigue	56 (21)	30 (20)	43 (23.6)	43 (28.5)
Diarrhea	47 (18)	19 (13)	36 (19.8)	7 (4.6)
Nausea	37 (14)	12 (8)	22 (12.1)	12 (7.9)
Asthenia	20 (8)	9 (6)	10 (5.5)	9 (6.0)
Insomnia	19 (7)	8 (5)	12 (6.6)	3 (2.0)
Dizziness	11 (4)	14 (9)	9 (4.9)	2 (1.3)
Back pain	11 (4)	8 (5)	12 (6.6)	8 (5.3)
Arthralgia	8 (3)	8 (5)	9 (4.9)	4 (2.6)
Abdominal pain	7 (3)	3 (2)	3 (1.6)	9 (6.0)
Irritability	7 (3)	4 (3)	4 (2.2)	8 (5.3)

	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX 12 Weeks	Placebo 12 Weeks	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks
SAEs				
Patients with ≥ 1 SAEs, n (%)	5 (1.9)	7 (4.6)	4 (2.2)	4 (2.6)
Description	Adrenal neoplasm, arteritis, cerebral hemorrhage, COPD, ovarian cancer, pneumonia, and seizure	AF, basal cell carcinoma, hepatic failure, schizophrenia, scrotal infection, subdural hematoma, and ventricular fibrillation	Cardiac failure congestive, abdominal hernia, toxicity to various agents, and intervertebral disc protrusion	Angina unstable, road traffic accident, lumbar spinal stenosis, and cerebrovascular accident
WDAEs				
AE leading to drug discontinuation, n (%)	1 (0.4)	3 (2.0)	0	1 (0.7)
Description	Angioedema due to ramipril	Increased hepatic enzymes, schizophrenia, or dizziness/chest pain/blurred vision/confusion		Headache
Deaths				
n (%)	0	0	2 (1.1)	0
Description			Cardiac arrest (due to combined heroin and fentanyl toxicity) and brain intraparenchymal hemorrhage	
Notable Harms				
Anemia	1 (0.4)	1 (0.7)	0	1 (0.7)
Pruritus	6 (2)	2 (1)	0	6 (4.0)
Increased bilirubin (Grade 3)	1 (0.4)	0	0	0
Increased ALT (Grade 3 or 4)	0	3 (2)	1 (0.5)	0
Hepatotoxicity	0	0	0	0
Hepatic decompensation or hepatic failure events	NR	NR	NR	NR
Hepatocellular carcinoma	1 (0.4)	0	0	0

AEs = adverse events; AF = atrial fibrillation; ARF = acute respiratory failure; ALT = alanine aminotransferase; COPD = chronic obstructive pulmonary disease; GP = glecaprevir / pibrentasvir; HCC = hepatocellular carcinoma; NR = not reported; SAE = serious adverse events; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir; WDAE = withdrawal due to adverse events.

[a] Frequency of at least 5% in any treatment group.
Source: Clinical Study Reports.[6,7]

Discussion

Summary of Available Evidence

Two pivotal phase III clinical trials were included in this review (POLARIS-1 and POLARIS-4). Both trials were randomized and multi-centre. POLARIS-1 was double blind, while POLARIS-4 was open-label. POLARIS-1 (N = 415) assessed the efficacy, safety, and tolerability of SOF/VEL/VOX for 12 weeks compared with placebo among patients with genotype 1, 2, 3, 4, 5, or 6 chronic HCV infection who had previously been treated with a DAA regimen containing an NS5A inhibitor. POLARIS-4 (N = 333) assessed the efficacy and safety of SOF/VEL/VOX and SOF/VEL for 12 weeks in DAA-experienced patients with genotype 1, 2, 3, or 4 chronic HCV infection who had not previously been treated with an NS5A inhibitor.

The main outcome in the included trials was the proportion of patients achieving SVR 12. The main limitation of the POLARIS-1 trial was the lack of an active treatment comparator group consisting of an existing treatment regimen for CHC. The POLARIS-4 trial was open-label, and awareness of treatment allocation might have influenced subjective measures such as HRQoL and reporting of AEs. The primary outcome in the POLARIS-1 and POLARIS-4 trials was compared with a performance goal; it was not clear how this threshold was chosen. However, there is currently another treatment (GP) that is indicated for the treatment of adult patients with HCV genotype 1 infection who were previously treated either with a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor (but not both classes of inhibitors). It is acknowledged, however, that GP is a new product that was not available during the design and conduct of the POLARIS-1 and POLARIS-4 trials. Patients with HIV coinfection were excluded from both trials. No patients who had undergone a transplant were included in the trials, and few patients with genotype 5 and 6 HCV infection were enrolled in the POLARIS-1 trial.

Interpretation of Results

Efficacy

The manufacturer is seeking reimbursement for SOF/VEL/VOX consistent with the Health Canada indication, i.e., for the treatment of chronic HCV infection in adult patients without cirrhosis or with compensated cirrhosis who have genotype 1, 2, 3, 4, 5, or 6 infection and who have previously been treated with an HCV regimen containing an NS5A inhibitor; or patients with genotype 1, 2, 3, or 4 infection who have been previously treated with an HCV regimen containing SOF without an NS5A inhibitor. The POLARIS-1 study included patients with genotypes 1, 2, 3, 4, 5, or 6 chronic HCV infection who had previously been treated with a DAA regimen containing an NS5A inhibitor, which was in line with the Health Canada–approved indication for SOF/VEL/VOX for the treatment of chronic HCV patients with genotype 1, 2, 3, 4, 5, or 6 infection who had previously been treated with an HCV regimen containing an NS5A inhibitor. The POLARIS-4 trial included DAA-experienced patients with genotypes 1, 2, 3, or 4 chronic HCV infection who had not received an NS5A inhibitor, which was in line with the Health Canada–approved indication for SOF/VEL/VOX for the treatment of chronic HCV patients with genotype 1, 2, 3, or 4 infection who had been previously treated with an HCV regimen containing SOF without an NS5A inhibitor.

Recently, the treatment of HCV-infected patients has evolved dramatically. Compared with the historic standard-of-care PR, the currently available options consist of all-oral, DAA-based regimens, many of which contain an NS5A inhibitor or SOF, require a shorter duration of treatment, are safer and more easily tolerated, and are more efficacious in clearing the virus, resulting in an approximately 95% chance of cure. As more patients are treated for HCV infection with these newer regimens, the number of patients who fail treatment will increase. Currently, there is only one other regimen (GP) that is indicated for patients previously treated either with a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor (but not both classes of inhibitors); however, it is limited only to the treatment of patients with genotype 1 HCV infection. On the other hand, GP has been approved for use in patients with ESRD, in whom treatment options may be limited, while SOF/VEL/VOX has not been approved for use in those with severe renal impairment or ESRD.

The POLARIS-1 trial patient population was comprised of NS5A inhibitor-experienced patients, a population that the clinical expert consulted by CDR considered to have an unmet need concerning safe and effective HCV treatment options. Because NS5A inhibitor-containing regimens constitute highly effective treatment, the patients who have failed these therapies can be anticipated to be difficult to achieve SVR in. In addition, greater than 40% of patients enrolled had cirrhosis. Per the study inclusion criteria, all patients were required to have received at least four weeks of prior treatment with a DAA and not to have discontinued their most recent regimen due to an AE or virologic failure due to noncompliance. The POLARIS-1 trial met its predefined primary efficacy end point, demonstrating that treatment with SOF/VEL/VOX for 12 weeks resulted in an SVR 12 rate of 96.2% (95% CI, 93.1% to 98.2%), which was statistically superior relative to the pre-specified performance goal of 85% ($P < 0.001$). No patients in the placebo 12-week group achieved SVR 12. Overall, 10 of 263 patients (3.8%) in the SOF/VEL/VOX 12-week group did not achieve SVR 12. Of these, one patient had virologic breakthrough, with pharmacokinetic data consistent with nonadherence, and six patients relapsed. All six patients who relapsed had cirrhosis, and four of the six patients had genotype 3 HCV infection, which is a more difficult genotype to treat effectively. Three additional patients did not achieve SVR 12 (two patients withdrew consent and one patient was lost to follow-up). Treatment with SOF/VEL/VOX resulted in SVR 12 rates that ranged from 90.9% to 100% in all subgroups. The SVR 12 rates in the SOF/VEL/VOX 12-week group were 93.4% (95% CI, 87.4% to 97.1%) in patients with cirrhosis, 94.9% (95%CI, 87.4% to 98.6%) in patients with genotype 3 HCV infection, and 92.9% (95% CI, 82.7% to 98.0%) in patients with genotype 3 HCV infection with cirrhosis. The SVR 12 rates were also higher than 93.8% regardless of prior DAA-class combinations (NS5A + NS5B inhibitor: 93.8% [95% CI, 88.9% to 97.0%], NS5A + NS3 inhibitor ± NS5B inhibitor: 100% [95% CI, 95.7% to 100.0%]) or specific regimens ([redacted]). There was a high prevalence of baseline RAVs among the enrolled DAA-experienced patients, and particularly NS5A RAVs. It seems that the persistence of these NS5A RAVs had no impact on the efficacy of SOF/VEL/VOX in the POLARIS-1 trial. No patient who relapsed following 12 weeks of SOF/VEL/VOX developed treatment-emergent RAVs.

The POLARIS-4 trial patient population was composed of non-NS5A inhibitor DAA-experienced patients with genotype 1 to 4 chronic HCV. Patients who had DAA exposure only to an NS3/4A protease inhibitor were excluded. Treatment with SOF/VEL/VOX for 12 weeks resulted in an SVR 12 rate of 97.8% (95% CI, 94.5% to 99.4%), with only one patient who relapsed. The SOF/VEL/VOX 12-week group met the primary efficacy end point of an SVR 12 rate that was statistically superior compared with the performance goal of 85% ($P <$

0.001). The SOF/VEL 12-week treatment group did not meet the primary efficacy end point, with an SVR 12 rate of 90.1% (95% CI, 84.1% to 94.3%) compared with the performance goal of 85% (*P* = 0.092). The study was not designed to compare between SOF/VEL/VOX and SOF/VEL treatment groups. The SVR 12 rates in the SOF/VEL/VOX 12-week group ranged from 95.7% to 100% across subgroups of interest. Within this treatment group, 46.2% of the patients had cirrhosis, 97.6% (95% CI, 91.7% to 99.7%) of whom achieved SVR 12. The SVR 12 rates were also high regardless of prior DAA experience. The majority of patients had prior DAA exposure to SOF or to SOF + SMV, and the SVR 12 rates for these patients were 97.7% (95% CI, 93.5% to 99.5%) and [redacted]% (95% CI, [redacted]% to [redacted]%), respectively. The SVR 12 rate in the SOF/VEL 12-week group (90.1%) was lower than that observed in the SOF/VEL/VOX 12-week group (97.3%). Seven of the 13 patients that did not achieve SVR 12 in the SOF/VEL 12-week group had genotype 3 HCV infection and cirrhosis; the SVR 12 rate in this subgroup was 76.7% (95% CI, 57.7% to 90.1%). For patients in the SOF/VEL/VOX 12-week group, 96.8% (95% CI, 83.3% to 99.9%) of patients with genotype 3 HCV infection and cirrhosis achieved SVR 12. The SVR 12 rates, overall and for most subgroups, were higher following 12 weeks of SOF/VEL/VOX treatment compared with 12 weeks of SOF/VEL treatment. In patients with genotype 1a HCV infection, the SVR 12 rates were 98.1% (95% CI, 90.1% to 100.0%) and 88.6% (95% CI, 75.4% to 96.2%) in the SOF/VEL/VOX 12-week and SOF/VEL 12-week groups, respectively. In patients with genotype 1b HCV infection, the SVR 12 rates were 95.8% (95% CI, 78.9% to 99.9%) and 95.5% (95% CI, 77.2% to 99.9%) in the SOF/VEL/VOX 12-week and SOF/VEL 12-week groups, respectively. In patients with genotype 2 HCV infection, the SVR 12 rates were 100.0% (95% CI, 88.8% to 100.0%) and 97.0% (95% CI, 84.2% to 99.9%) in the SOF/VEL/VOX 12-week and SOF/VEL 12-week groups, respectively. In patients with genotype 3 HCV infection, the SVR 12 rates were 94.4% (95% CI, 87.3% to 99.5%) and 84.6% (95% CI, 71.9% to 93.1%) in the SOF/VEL/VOX 12-week and SOF/VEL 12-week groups, respectively. For patients with genotype 4 HCV infection, 100% (95% CI, 82.4% to 100.0%) of patients in the SOF/VEL/VOX 12-week group achieved SVR 12. Among cirrhotic patients, the SVR 12 in the SOF/VEL/VOX 12-week group was also higher compared with the SOF/VEL 12-week group (97.6% [95% CI, 91.7% to 99.7%] versus 85.5% [95%CI, 75.0% to 92.8%]). However, no statistical comparison was undertaken between treatment groups. It seems that there was no impact of baseline RAVs on SVR 12 for patients in the SOF/VEL/VOX 12-week or SOF/VEL 12-week groups. The single patient who relapsed in the SOF/VEL/VOX 12-week group did not have any treatment-emergent RAVs. However, 10 of the 14 patients in the SOF/VEL 12-week group did have treatment-emergent RAVs, all of whom had NS5A variants at the Y93 position.

Both POLARIS studies demonstrated that SOF/VEL/VOX for 12 weeks is effective in achieving high SVR 12 results across the range of HCV genotypes and in patients with a range of DAA treatment experience.

The CDR review protocol also included subgroup by HIV or hepatitis B coinfection, renal insufficiency, decompensated liver disease, and liver transplant; however, such subgroup analyses were not undertaken because patients who would fall into each of these subgroups were excluded from the trial. As a result, the efficacy and safety of SOF/VEL/VOX in these subgroups of patients is still unknown.

The key limitation of the available evidence was the lack of head-to-head comparative data, as the POLARIS-1 trial did not include another DAA-based regimen as a randomized control group, and the POLARIS-4 trials did not compare SOF/VEL/VOX treatment with SOF/VEL treatment. Both trials assigned some patients to groups non-randomly, primarily for patients

with genotypes for which the prevalence is relatively lower. Importantly, there were no data comparing SOF/VEL/VOX with GP, which is indicated for patients previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor (but not both classes of inhibitors). However, this indication is only limited to the treatment of patients with genotype 1 HCV infection, although such comparison may not have been feasible given the rapid pace of development of treatments for hepatitis C.

The POLARIS-4 trial was open-label, and awareness of treatment allocation may have influenced subjective measures such as quality of life and reporting of AEs. The trials evaluated SVR 12, which is a key outcome; however, neither trial was designed to assess longer-term outcomes such as hepatic-related morbidity or mortality, which are important to patients. Both trials evaluated patient-reported outcomes as exploratory. The instruments used in both trials included the SF-36, the CLDQ-HCV, the FACIT-F, and the WPAI: Hepatitis C. Between-group statistical comparisons were conducted; however, no statistically significant differences were detected between SOF/VEL/VOX and the placebo (except for the CLDQ-HCV at final treatment visit) or SOF/VEL for the instruments tested. Patient-reported outcomes reported in the trials were difficult to interpret due to limitations in the data, including the open-label design (in POLARIS-4), missing data, the analysis methods used (i.e., no imputation of missing data or control of multiplicity).

Harms

In general, the majority of patients experienced one or more AEs, with headache, fatigue, diarrhea, and nausea reported most frequently among those who received SOF/VEL/VOX. In the double-blind, placebo-controlled trial (POLARIS-1), 78% and 70% of patients reported AEs in the SOF/VEL/VOX and placebo groups, respectively. Overall, 77% and 74% of patients in the SOF/VEL/VOX and SOF/VEL 12-week groups, respectively, reported AEs in the POLARIS-4 randomized controlled trial

In the POLARIS-1 trial, the incidence of SAEs in the placebo 12-week group was 4.6%, which was more than double that reported in the SOF/VEL/VOX 12-week group (1.9%). One patient in the placebo 12-week group experienced an AE that led to interruption of the study drug , and four patients (one patient receiving SOF/VEL/VOX and three patients receiving placebo) permanently discontinued the study drug due to AEs. No patients died during the study. In the SOF/VEL/VOX 12-week group, no patients had grade 3 or 4 elevated ALT compared with three patients with grade 3 or 4 ALT elevations in the placebo 12-week group. A grade 3 increase in total bilirubin was reported in one patient in the SOF/VEL/VOX 12-week group. There was no evidence of VOX-related hepatotoxicity.

In the POLARIS-4 trial, the incidences of SAEs were similar in the SOF/VEL/VOX 12-week (2.2%) and the SOF/VEL 12-week (2.6%) groups. One patient in the SOF/VEL 12-week group experienced an AE that led to premature discontinuation of study drug, and one patient in the SOF/VEL/VOX 12-week group died of an illicit drug overdose two days after the last dose of study drug. Only one grade 3 elevated ALT was observed in a patient in the SOF/VEL/VOX 12-week group. This patient also had baseline grade 3 increased total bilirubin and increased aspartate aminotransferase, and all of these abnormalities were likely explained by ongoing heavy alcohol use, per the investigator. No other grade 3 or 4 chemistry laboratory abnormalities of increased ALT or total bilirubin were observed in this study. There was no evidence of VOX-related hepatotoxicity

Of the included trials, only the POLARIS-1 trial was double blind, and the reporting of AEs may have been influenced by the patient's knowledge of the treatment received in the open-

label POLARIS-4 trial. The lack of an active control group in the POLARIS-1 trial is an important limitation to the available safety data. Moreover, the trials were not designed to assess the longer-term safety of SOF/VEL/VOX. All of the trials excluded patients with hepatitis B coinfection; thus, the trials provide no data on the risk of hepatitis B reactivation, which is listed as a warning on the product monograph.[4] SOF/VEL/VOX also has a number of potentially clinically important drug-drug interactions that may affect the risk of AEs or reduce the therapeutic effect of SOF/VEL/VOX.[4] While results from observational studies indicate that risk of HCC was considerably reduced after achieving SVR using interferon-based or DAA treatment, both trials were not long enough to assess such association.[37,38]

Potential Place in Therapy[2]

Significant progress has been made in the treatment of HCV around the world since 2014.[5] DAA treatment regimens have revolutionized the ability to provide safe and effective therapy to the majority of patients with HCV, with SVR rates of more than 90% for all genotypes and stages of liver disease.[5] However, there is a population of HCV patients for whom treatment with a DAA regimen was unsuccessful and there are few options for a cure. Currently, there is one Health Canada–approved DAA regimen available for use in patients who have failed prior DAA therapy; however, the treatment duration is 16 weeks.

SOF/VEL/VOX has been recently approved by Health Canada and now meets the need of this population. SOF/VEL/VOX is a pan-genotypic DAA regimen that has been shown in several phase III studies to result in SVR in more than 95% of patients with previous DAA failure after 12 weeks of treatment with minimal side effects. Therefore, in clinical practice, SOF/VEL/VOX would be considered in patients with HCV with compensated liver disease (including compensated cirrhosis), regardless of genotype, who have failed a prior DAA regimen. Given that the ability to achieve SVR in the phase III trials was not related to the presence of resistant variants, no special diagnostic tests would be required prior to consideration of therapy.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

A 12-week regimen of SOF/VEL/VOX was associated with a high percentage of patients achieving SVR 12, with point estimates of 96.2% in the POLARIS-1 trial, which included patients with genotypes 1, 2, 3, 4, 5, or 6 chronic HCV infection who had previously been treated with DAA regimens containing an NS5A inhibitor, and 97.8% in the POLARIS-4 trial, which included DAA-experienced patients with genotypes 1, 2, 3, or 4 HCV chronic HCV infection who had not received an NS5A inhibitor. High rates of SVR 12 were observed across several subgroups of interest. The SVR 12 rates for SOF/VEL/VOX in POLARIS-1 and POLARIS-4 were statistically superior relative to the pre-specified performance goal of 85%. The presence of baseline RAVs did not impact the treatment outcome in the SOF/VEL/VOX 12-week group.

HRQoL, fatigue, and work productivity were evaluated as exploratory outcomes in the trials using the SF-36, the CLDQ-HCV, the FACIT-F questionnaire, and the WPAI: Hepatitis C. No conclusions could be drawn for these outcomes due to limitations in the data, which included an open-label study design (in the case of the POLARIS-4 trial) and the analysis methods used. Headache, fatigue, diarrhea, and nausea were reported most frequently among those who received SOF/VEL/VOX. None of the trials was designed to assess longer-term outcomes such as hepatic-related morbidity or mortality, which are important to patients.

Overall, data from the POLARIS trials demonstrated that SOF/VEL/VOX for 12 weeks was effective in treating patients included in the studies, with no apparent serious safety signal over this time period.

The key limitation was the limited comparative data. In particular, there were no comparative data versus GP, which is indicated for patients previously treated either with a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor; however, the indication for GP is limited to treatment-experienced patients with genotype 1 HCV infection. Patients from important subgroups who may be more difficult to treat (e.g., those with HIV coinfection or who have had a liver transplant) were excluded from the trials, and thus the generalizability of the studies' findings to these patients may be limited. Data were scarce for those with genotype 5 and 6 HCV infection, although globally, the prevalence of these viral variants in most regions is low.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

Five groups submitted patient input for this review.

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 awareness, fundraising, and outreach efforts. The CLF has received unrestricted educational grants from AbbVie Corporation, Astellas Pharma Canada Inc., Boehringer Ingelheim (Canada) Inc., Gilead Sciences Canada Inc., Janssen Inc., Merck Canada Inc., Novartis Pharmaceuticals Canada Inc., and Hoffmann-La Roche Limited.

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization that addresses access to treatment, care, and support for people living with HIV and hepatitis C. Full membership is limited to persons living with HIV, including patients with hepatitis C virus (HCV) coinfection or organizations with a substantial HIV mandate. CTAC received unrestricted organizational and educational grants from Gilead Sciences and ViiV Healthcare in the 2017-2018 fiscal years..

The Hepatitis C Education and Prevention Society (HepCBC) is a non-profit organization run by and for people affected by HCV in British Columbia. They focus on providing peer support, anti-stigma activities, prevention education, and general hepatitis information to the general public, and particularly to baby-boomer, Indigenous, and immigrant communities and those living in rural and remote locations. In addition, they encourage HCV and hepatitis B testing among at-risk groups. HepCBC has received funding for hepatitis C–oriented projects such as publishing educational materials, organizing educational forums, attending and presenting at educational conferences, advertising in newspapers (for events and to increase hepatitis C patient awareness), and holding awareness activities conducted over the last four years by Merck Pharmaceuticals, Lupin Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, and AbbVie, with support from Rx&D, the pharmaceutical umbrella organization. The authors of this submission attended conferences and meetings that were funded by the aforementioned pharmaceutical companies.

The Pacific Hepatitis C Network's mission is to strengthen the capacity of individuals and organizations throughout British Columbia to prevent new HCV infections and improve the health and treatment outcomes of people already living with HCV. Its members include individuals who are HCV antibody–positive, at risk, or concerned about HCV. The Pacific Hepatitis C Network has received funding from AbbVie, Bristol-Myers Squibb and Gilead Science in the past two years.. The manufacturer-provided information about the sofosbuvir/velpatasvir/voxilaprevir clinical trial data that was used to complete the submission.

The Centre Associatif Polyvalent d'Aide Hépatite C (CAPAHC) is focused on the fight against hepatitis C and HIV coinfection in Quebec. CAPAHC communicates with patients with hepatitis C through monthly support groups, information, and crisis lines, and provides training programs for professionals working with those who may be affected by hepatitis C and HIV. CAPAHC also provides treatment support for those who are disaffiliated, take drugs, or are involved in the sex trade. CAPAHC has received support from the Public

Health Agency of Canada, Agence de la Santé et des Services Sociaux de Montréal, AbbVie, Gilead, and Merck.

2. Condition-Related Information

The information was gathered through interviews with patients and care givers affected by hepatitis C, health care professionals, and organizations' staff or volunteers, as well as surveys, social media, meetings with support groups, informal discussions, and a webinar that included patients diagnosed with hepatitis C. Information gathered from previous patient input consultations from other hepatitis C drugs was used as well.

Hepatitis C is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, hepatocellular carcinoma, liver failure, and hepatic encephalopathy. Data from Health Canada (2011) suggest that approximately 245,000 Canadians are presently infected with HCV, with as many as 44% of those individuals unaware that they are living with the virus. The symptoms of hepatitis C include fatigue, nausea, headaches, sensitivities to light and food, memory loss, mood swings, itchy skin, abdominal pain, severe joint and muscle pain, portal hypertension, sleeplessness, slowed reflexes, psoriasis, peripheral neuropathy, osteopenia, diarrhea, and muscle wasting. Hepatitis C patients also report experiencing psychological and emotional stress, as well as social isolation. Patients are reluctant to talk about their disease for fear of being judged by those closest to them. The stigma associated with HCV infection can lead to misperceptions and fear among family, friends, and co-workers, and personal relationships could deteriorate or disappear completely. One patient in stated that "…whenever I have told people about my condition it was always met with criticism, fear and rejection. People seem to 'know all about it' when, in fact they do not."

The symptoms may be severe and can limit patients' ability to work, manage their home, care for family members, and maintain friendships. The symptoms and impact of hepatitis C patients describe ranged from asymptomatic to "Symptoms such as insomnia, tiredness, itchiness, poor circulation, constipation and fear of accidently infecting someone else makes day to day life difficult…" and the inability to concentrate or remember. The fatigue and "brain fog" can be unrelenting, and – nothing helps – no amount of sleep, coffee, activity, walks or rest makes it better. These symptoms are non-specific and "extra-hepatic," so very often physicians do not make the link between the symptoms and their hepatitis C, or may minimize them.

A large proportion of people living with HIV infection are co-infected with HCV. In 2007, the Public Health Agency of Canada estimated that 20% of people living with HIV are co-infected with hepatitis C. The presence of both viruses may exacerbate the liver disease progression, and many of their respective medications impact one another.

For caregivers (spouses, parents, and adult children), the challenges associated with caring and achieving a cure for hepatitis C patients are significant. They have described caring for a hepatitis C patient undergoing treatment as a relentless and ongoing task. The symptoms of advanced hepatitis C can leave the patient completely dependent and unable to contribute financially, physically, psychologically, or emotionally to the household or their relationship. 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 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. One caregiver stated, "I had to manage the household responsibilities with help from our daughter. My husband's mental changes were

hugely apparent. At sundown, all he wanted to do was sleep and dealing with him was like talking to an eight year old child at times… He developed shaking hands that would cramp so badly at times that he couldn't hold a fork to eat. He also couldn't be left alone because his esophageal varices put him at high risk of severe bleeding."

3. Current Therapy Related Information

In recent years, direct-acting antiviral agents (DAAs) become available to treat patients with hepatitis C, offering the advantage of higher efficacy rates and reduced side effects compared with the former standard therapy, pegylated interferon plus ribavirin for up to 48 weeks. Several all-oral treatments for HCV have been approved, both federally and provincially. Interferon-free treatment options include sofosbuvir/ledipasvir (Harvoni), ombitasvir/paritaprevir/ritonavir + dasabuvir (Holkira Pak), sofosbuvir/velpatasvir (Epclusa), grazoprevir/elbasvir (Zepatier), and ombitasvir/paritaprevir/ritonavir (Technivie). They offer patients a low pill burden, few side effects, a shorter treatment length (12 weeks), and efficacy rates of 90% or higher.

Many patients from CTAC expressed optimism about the promising benefits related to the use of DAAs when they were asked about the potential of these medications as they were beginning to roll out in Canada. Benefits of DAAs included that they were easier to take, required fewer pills, did not require injections, and offered shorter treatment times. As new DAAs have become available, caregivers have noted that while side effects are not uncommon with newer treatments, they were generally considered milder and more tolerable than those associated with peg-interferon and ribavirin. With respect to one patient, a caregiver stated, "When he underwent his third attempt at a cure, all side effects were manageable and so much less than any other regimen, despite his F4 cirrhosis and increasing MELD and symptoms… the dosing regimen was easy to administer and tolerate… the first was very difficult, the second try almost led to his death."

Currently, the biggest barrier to treatment with the new DAA combinations is their high cost, and treatment rates remain low. Accessing treatments may be challenging, particularly for patients with multiple barriers or minimal liver damage. Patients in rural and remote areas, in particular, may have difficulty in accessing a hepatitis specialist.

4. Expectations about the Drug being Reviewed

None of the patient groups were able to obtain feedback from a patient who had sofosbuvir/velpatasvir/voxilaprevir. Information about sofosbuvir/velpatasvir/voxilaprevir was obtained through consultation with physicians who had treated hepatitis C patients with this drug or published literature.

Although cure rates have improved significantly with all-oral DAA regimens, not all patients achieve a cure, and treatment options for these patients have been limited. Sofosbuvir/velpatasvir/voxilaprevir represents a viable re-treatment option for patients who have failed treatment with other DAAs, and specifically genotype 1-6 patients who have taken a nonstructural viral protein 5A (NS5A) inhibitor (found in Harvoni, Holkira Pak, and Technivie) and genotype 1 to 4 patients who were treated with a non-NS5A regimen (e.g., sofosbuvir without an NS5A inhibitor). Expectations of sofosbuvir/velpatasvir/voxilaprevir are that it will be very well tolerated and effective for all genotypes, regardless of resistance or the presence of cirrhosis. No ribavirin is required to achieve high cure rates, which is not true of some other DAA-based regimens used in this difficult-to-treat patient group. The pill burden is low (one pill a day for 12 weeks). The adverse effects reported in clinical trials

appear to be similar to those reported with other DAA regimens and include headache, fatigue, diarrhea, and nausea. Few patients stopped treatment due to adverse effects.

There is some urgency to find a treatment option for patients who have failed to respond to other DAA agents, as these patients were already quite sick when qualifying for their initial treatment. Knowing that there is a treatment option available, if first-line therapies fail, would help alleviate some patients' stress and anxiety. Patients want access to treatments with shorter treatment times, fewer side effects, higher cure rates, the ability to work while being treated, and that cure patients who have already been treated without success. There is hope that the treatments will become available to them without them first having to get sicker.

HepCBC noted the recent investigation into the possibility of hepatitis B virus reactivation among HCV patients taking the new interferon-free DAA treatments. They suggested that all HCV patients about to embark on an all-oral regime should have their hepatitis B virus status confirmed prior to starting treatment. HepCBC also noted that research has indicated a possible recurrence of liver cancer following (third generation) DAA treatment. Hepatocellular carcinoma is a factor that must be considered carefully before a treatment regimen is prescribed, at least until more data becomes available.

CLF stated that "…therapy is only as good as the access to it. Sofosbuvir/velpatasvir/voxilaprevir would be a good addition to the arsenal treating physicians can use to care for their most difficult-to-treat patients. For this treatment to have maximum impact however, it must be available to all patients who need it." CAPAHC sees the drug as valuable for those who have been unsuccessful on other treatments in the global effort to eradicate HCV.

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:	August 28, 2017
Alerts:	Weekly search updates until December 13, 2017
Study Types:	No search filters were applied
Limits:	No date or language limits were used

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
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.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	(vosevi* or (sof adj2 vel adj2 vox) or S900007740).ti,ab,ot,kf,hw,rn,nm.
2	(sofosbuvir* or sof or GS-7977* or GS7977* or Hepcnat* or Hepcvir* or PSI-7977* or PSI7977* or resof* or HSDB 8226* or HSDB8226* or sovaldi* or sovihep* or WJ6CA3ZU8B or 1190307-88-0).ti,ab,hw,ot,kf,rn,nm.
3	(velpatasvir* or vel or GS5816* or GS-5816* or 1377049-84-7 or 1458063-71-2 or KCU0C7RS7Z).ti,ab,ot,kf,rn,nm,hw.
4	(voxilaprevir* or vox or GS9857* or GS-9857* or 1535212-07-7 or 1929654-80-7 or 0570F37359).ti,ab,ot,kf,hw,rn,nm.
5	2 and 3 and 4
6	epclusa*.ti,ab,hw,ot,kf,rn,nm.
7	4 and 6
8	1 or 5 or 7
9	8 use ppez
10	*vosevi/
11	(vosevi* or (sof adj2 vel adj2 vox) or S900007740).ti,ab,kw,tn.
12	(sofosbuvir* or sof or GS-7977* or GS7977* or Hepcnat* or Hepcvir* or PSI-7977* or PSI7977* or resof* or HSDB 8226* or HSDB8226* or sovaldi* or sovihep* or WJ6CA3ZU8B or 1190307-88-0).ti,ab,kw.
13	(velpatasvir* or vel or GS5816* or GS-5816* or 1377049-84-7 or 1458063-71-2 or KCU0C7RS7Z).ti,ab,kw.
14	(voxilaprevir* or vox or GS9857* or GS-9857* or 1535212-07-7 or 1929654-80-7 or 0570F37359).ti,ab,kw.
15	12 and 13 and 14
16	10 or 11 or 15
17	epclusa*.ti,ab,kw.
18	14 and 17
19	16 or 18
20	19 use oemezd
21	9 or 20
22	remove duplicates from 21

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. 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:	August 2017
Keywords:	Drug names, Indication
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 searching health-related grey literature* (https://www.cadth.ca/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
Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, et al. Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. Gastroenterology. 2017 Jul;153(1):113-22.	Inappropriate treatment duration

Appendix 4: Detailed Outcome Data

Table 11: Virologic Response by Subgroup

	POLARIS-1[a]	POLARIS-4	
	SOF/VEL/VOX 12 Weeks	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks
	N = 263	N = 182	N = 151
SVR 12 n/N (%) [95% CI]	253/263 (96.2) [93.1, 98.2]	178/182 (97.8) [94.5, 99.4]	136/151 (90.1) [84.1, 94.3]
P value (compared with performance goal of 85%)	0.001	0.001	0.092
Reason for nonresponse			
Overall virologic failure, N (%)	7 (2.7)	1 (0.5)	15 (9.9)
On-treatment virologic failure	1 (0.4)	0	1/151 (0.7)
Relapse	6/261 (2.3)	1/182 (0.5)	14/150 (9.3)
Other	3 (1.1)	3/182 (1.6)	0
Discontinued study drug prematurely	1 (0.4)	0	0
Lost to follow-up	1 (0.4)	2 (1.1)	0
Withdrew consent	1 (0.4)	0	0
Death	0	1 (0.5)	0
SVR 12 by subgroup			
Genotype			
1	146/150 (97.3)	76/78 (97.4)	60/66 (90.9)
1a	97/101 (96.0)	53/54 (98.1)	39/44 (88.6)
1b	45/45 (100)	23/24 (95.8)	21/22 (95.5)
2	5/5 (100)	31/31 (100.0)	32/33 (97.0)
3	74/78 (94.9)	52/54 (96.3)	44/52 (84.6)
4	20/22 (90.9)	19/19 (100.0)	0/0
5	1/1 (100)	0/0	0/0
6	6/6 (100)	0/0	0/0
Cirrhosis			
Yes	113/121 (93.4)	82/84 (97.6)	59/69 (85.5)
No	140/142 (98.6)	96/98 (98.0)	77/82 (93.9)
Prior HCV therapy, n/N (%)			
DAA naive	0/0	0/0	1/1 (100.0)
NS5B only	0/0	131/134 (97.8)	99/109 (90.8)
NS5B + NS3	0/0	45/46 (97.8)	33/38 (86.8)
NS5A + NS5B	151/161 (93.8)	0/0	0/0
NS5A + NS3 ± NS5B	83/83 (100)	0/0	0/0
NS5A ± other	18/18 (100)	0/0	0/0
Other	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

	POLARIS-1[a]	POLARIS-4	
	SOF/VEL/VOX 12 Weeks	SOF/VEL/VOX 12 Weeks	SOF/VEL 12 Weeks
	N = 263	N = 182	N = 151
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
HCV RNA (IU/mL)			
< 800,000	69/73 (94.5)	44/46 (95.7)	35/38 (92.1)
≥ 800,000	184/190 (96.8)	134/136 (98.5)	101/113 (89.4)

CI = confidence interval; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; NS3 = nonstructural viral protein 3; NS5A = nonstructural viral protein 5A; NS5B = nonstructural viral protein 5B; RNA = ribonucleic acid; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir; SVR 12 = sustained virologic response 12 weeks after the end of treatment.

[a] The placebo group was not presented because zero patients achieved virologic response.

Source: Clinical Study Reports.[6,7]

Table 12: Health-Related Quality of Life

	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX 12 Weeks N = 263	Placebo 12 Weeks N = 152	SOF/VEL/VOX 12 Weeks N = 182	SOF/VEL 12 Weeks N = 151
SF-36				
Physical Component Score				
Baseline				
N	257	150	179	150
Mean (SD)	49.6 (9.03)	48.0 (9.55)	48.4 (9.03)	48.4 (9.17)
Final treatment visit				
N	255	150	179	150
Mean (SD) change from baseline	0.3 (6.30)	0.6 (6.24)	0.5 (6.58)	0.6 (6.53)
Between-group difference (95% CI)	NR		NR	
P value	0.73		0.91	
Follow-up week 12				
N	250	NR	174	145
Mean (SD) change from baseline	0.9 (6.57)	NR	1.2 (6.89)	1.5 (5.96)
Between-group difference (95% CI)	NR		NR	
P value	NR		0.99	
Mental Component Score				
Baseline				
N	257	150	179	151
Mean (SD)	49.2 (10.26)	49.9 (10.12)	47.8 (11.15)	48.3 (10.23)
Final treatment visit				
N	255	150	179	151
Mean (SD) change from baseline	0.2 (9.67)	-1.2 (6.90)	1.0 (8.69)	-0.4 (9.78)
Between-group difference (95% CI)	NR		NR	
P value	0.094		0.12	
Follow-up week 12				

	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX 12 Weeks N = 263	Placebo 12 Weeks N = 152	SOF/VEL/VOX 12 Weeks N = 182	SOF/VEL 12 Weeks N = 151
N	250	NR	174	146
Mean (SD) change from baseline	1.9 (9.34)	NR	2.6 (8.89)	1.9 (9.55)
Between-group difference (95% CI)	NR		NR	
P value	NR		0.73	
CLDQ-HCV				
Overall Score				
Baseline				
N	256	150	178	149
Mean (SD)	5.3 (1.10)	5.2 (1.19)	5.1 (1.12)	5.1 (1.16)
Final treatment visit				
N	255	150	178	149
Mean (SD) change from baseline	0.2 (0.80)	0.0 (0.71)	0.3 (0.85)	0.2 (0.78)
Between-group difference (95% CI)	NR		NR	
P value	0.008		0.30	
Follow-up week 12				
N	250	NR	173	146
Mean (SD) change from baseline	0.4 (0.82)	NR	0.5 (0.90)	0.5 (0.89)
Between-group difference (95% CI)	NR		NR	
P value	NR		0.97	

CLDQ-HCV = Chronic Liver Disease Questionnaire-HCV; CI = confidence interval; HCV = hepatitis C virus; NR = not reported; SD = standard deviation; SF-36 = 36-Item Short Form Survey Instrument; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir.

P value based on Wilcoxon rank sum test.

Source: Clinical Study Reports.[6,7]

Table 13: Other Patient-Reported Outcomes

	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX 12 weeks N = 263	Placebo 12 weeks N = 152	SOF/VEL/VOX 12 weeks N = 182	SOF/VEL 12 weeks N = 151
FACIT-F				
Total Score				
Baseline				
N	249	149	176	148
Mean (SD)	121.4 (26.4)	118.7 (28.52)	116.2 (27.99)	117.7 (26.75)
Final treatment visit				
N	248	149	176	148
Mean (SD) change from baseline	1.4 (18.51)	–0.6 (17.13)	3.7 (20.54)	1.9 (18.59)
Between-group difference (95% CI)	NR		NR	
P value	0.39		0.47	
Follow-up week 12				
N	240	NR	171	141

	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX 12 weeks N = 263	Placebo 12 weeks N = 152	SOF/VEL/VOX 12 weeks N = 182	SOF/VEL 12 weeks N = 151
Mean (SD) change from baseline	6.3 (20.11)	NR	8.2 (20.14)	7.1 (20.87)
Between-group difference (95% CI)	NR		NR	
P value	NR		0.94	
WPAI: Hepatitis C				
% Overall Work Impairment due to HCV				
Baseline				
N	137	79	104	83
Mean (SD)	11.9 (21.35)	18.8 (27.54)	17.0 (24.61)	15.2 (21.83)
Final treatment visit				
N	126	73	104	79
Mean (SD) change from baseline	2.1 (23.49)	–3.3 (17.19)	0.3 (25.39)	2.7 (21.31)
Between-group difference (95% CI)	NR		NR	
P value	0.13		0.40	
Follow-up week 12				
N	115	NR	91	70
Mean (SD) change from baseline	0.0 (16.08)	NR	–4.7 (25.40)	–7.2 (22.24)
Between-group difference (95% CI)	NR		NR	
P value	NR		0.68	
% Activity Impairment due to HCV				
Baseline				
N	247	145	173	147
Mean (SD)	18.3 (26.29)	20.7 (28.25)	21.6 (25.01)	23.2 (27.12)
Final treatment visit				
N	243	145	173	147
Mean (SD) change from baseline	–1.8 (22.98)	–1.0 (23.59)	–3.5 (24.13)	–2.4 (25.86)
Between-group difference (95% CI)	NR		NR	
P value	0.23		0.43	
Follow-up week 12				
N	236	NR	160	142
Mean (SD) change from baseline	–5.4 (20.57)	NR	–8.4 (24.46)	–8.9 (26.73)
Between-group difference (95% CI)	NR		NR	
P value	NR		0.87	

CI = confidence interval; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HCV = hepatitis C virus; NR = not reported; SD = standard deviation; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir; SD = standard deviation; WPAI: Hepatitis C = Work Productivity and Activity Impairment Questionnaire, Hepatitis C.

P value based on Wilcoxon rank sum test.

Clinical Study Reports.[6,7]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

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

Findings

The above outcome measures are briefly summarized in Table 14.

Table 14: Validity and Minimum Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity[a]	MCID	References
SF-36	Generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life	Yes	HCV: Unknown General use: 2 to 4 per domain or 2 to 3 points for component scores	Ware et al.[29]
CLDQ-HCV	The CLDQ is a health-related quality of life instrument for patients with chronic liver disease.	Yes	HCV: Unknown	Younossi et al.[30]
FACIT-F	Assesses self-reported fatigue, including feelings of tiredness, listlessness, and energy as well as fatigue's impact on daily activities and function	No	HCV: Unknown RA: 3 to 4 points	Webster et al.[32]
WPAI: Hepatitis C	The WPAI is an instrument used to measure the impact of a disease on work and daily activities.	No	HCV: Unknown Crohn's: 7%	Reilly et al.[39]

CLDQ-HCV = Chronic Liver Disease Questionnaire-HCV; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HCV = hepatitis C virus; MCID = minimal clinically important difference; RA = rheumatoid arthritis; SF-36 = 36-Item Short Form Survey Instrument; WPAI: Hepatitis C = Work Productivity and Activity Impairment Questionnaire, Hepatitis C

[a] In patients with Hepatitis C.

Short Form 36 Item Instrument

The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life (HRQoL). SF-36 consists of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. SF-36 also provides two component summaries: the physical component summary (SF-36 PCS) and the mental component summary (SF-36 MCS), which are created by aggregating the eight domains. The SF-36 PCS, SF-36 MCS, and eight domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of the SF-

36, a change of 2 to 4 points in each domain or 2 to 3 points in each component summary indicates a clinically meaningful improvement, as determined by the patient.[29]

A systematic review was conducted to identify and provide information on HRQoL instruments for hepatitis C.[40] 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 15).[40]
- A panel of experts was convened to estimate the minimal clinically important difference (MCID) in hepatitis C indirectly based upon existing HRQoL data.[40] 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 (with a range of 3 to 5) on the SF-36 vitality scale, with a corresponding effect size of 0.2 (with a range 0.15 to 0.25).[40] MCIDs for other dimensions or for the two component scores were not estimated. Of note, this study did not use an anchor-based method, which may be preferred, to generate the MCID and, as a result, it is unclear if the estimates represent values patients would identify as clinically important.[41]

No MCID estimates in patients with chronic hepatitis C (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 hepatitis C virus (HCV).

Table 15: 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

Source: Spiegel et al. 2005.[40]

Work Productivity and Activity Impairment Questionnaire, Hepatitis C

The WPAI questionnaire is used to measure the impact of a disease on work and daily activities and consists of six questions: Q1 = currently employed; Q2 = hours missed due to health problems; Q3 = hours missed other reasons; Q4 = hours actually worked; Q5 = degree health affected productivity while working (using a 0 to 10 Visual Analogue Scale);

Q6 = degree health affected productivity in regular unpaid activities.[34,39,42] The questionnaire elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing of work was challenging, and the extent to which the patient was limited at work (i.e., experienced work impairment) during the past 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 a worker's compensation days) and impairment due to decreased productivity while at work (reduced performance of productivity while at work due to health reasons, including time not being on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work. Four main outcomes can be generated from the WPAI and expressed in percentages by multiplying the following scores by 100: 1) per cent work time missed due to health = Q2/(Q2 + Q4) for those who were currently employed; 2) per cent impairment while working due to health = Q5/10 for those who were currently employed and actually worked in the past seven days; 3) per cent overall work impairment due to health = Q2/(Q2 + Q4) + (1 - Q2/[Q2 + Q4]) × (Q5/10) for those who were currently employed; and 4) per cent activity impairment due to health = Q6/10 for all respondents. For those who missed work and did not actually work in the past seven days, the per cent overall work impairment due to health would be equal to the per cent work time missed due to health. The scores are presented as a percentage, with lower values indicating better quality of life.[34,42]

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.[43]

Although no information on the validity of the WPAI or its MCID in hepatitis C patients was found, the MCID for the WPAI has been reported to be ≥ 7 percentage points in patients suffering from Crohn's disease.[34]

Chronic Liver Disease Questionnaire-Hepatitis C Virus

The CLDQ-HCV is an HRQoL instrument for patients with hepatitis C. The questionnaire was developed by Younossi et al. using a variety of sources, including available generic and liver-specific instruments (mainly the CLDQ-HCV), interviews, and focus groups with hepatitis C patients.[44] The final instrument was derived from administering an initial questionnaire containing 77 items to 72 patients with CHC, and eliminating redundancies following impact scores and factor analysis. Approximately half of the questions in the CLDQ-HCV also occur in the CLDQ, with the remaining questions focusing on symptoms and issues unique to HCV. Both the CLDQ-HCV and the CLDQ are anchored by a two-week recall period. Each item on the CLDQ-HCV questionnaire is open ended and may be answered with one of seven response options rated on a Likert scale from 1 to 7. A score of 1 means the symptom being assessed is "present always," while a score of 7 means the symptom is "never present." Therefore, a higher score corresponds to a better HRQoL, while a lower score corresponds to a worse HRQoL. The instrument has 29 items in four domains: activity/energy, emotional, worry, and systemic.[30] The domain score is the sum of the item scores for that domain, divided by the number of items in that respective domain.[30] The overall CLDQ score is the mean of the domain scores.[30]

The psychometric properties of the CLDQ-HCV were evaluated for 4,142 hepatitis C patients enrolled in sofosbuvir clinical trials. High internal consistency was noted, with Cronbach alpha coefficients ranging from 0.84 for the systemic domain to 0.94 for the

emotional domain.[30] The instrument showed discriminant power, with strong associations between lower CLDQ-HCV domain scores in patients with cirrhosis, a history of failed HCV treatment, depression, and clinically overt fatigue.[30] Of note, the domain scores were skewed toward the highest possible values, with 43% to 59% of domain values equal to 7 (the best score). Less than 0.1% and < 2% of domain scores were 1 or 2 respectively.[30]

The activity/energy domain was strongly correlated with the SF-36 vitality (R = 0.82) and the physical domain (R = 0.80), and the correlation was lowest for the mental health domain (R = 0.65).[30] The emotional domain was highly correlated with the SF-36 mental health summary score (R = 0.81) but less so with the physical functioning domain (R = 0.47). The worry domain had a lower correlation with the SF-36 domains (0.39 to 0.56), which was to be expected, as worry may not be well captured by the SF-36. The correlations ranged from 0.57 to 0.72 for the systemic domain, and from 0.59 to 0.77 for the overall CLDQ-HCV score relative to the SF-36 domains.[30] In two other abstracts, the CLDQ-HCV was validated against SF-36 in hepatitis C patients. The highest correlations were found for the activity/energy domain and the SF-36 physical function (0.78 to 0.84) and for the emotional domain versus the SF-36 mental health (0.58) and the MCS (0.59).[45,46]

Responsiveness was tested in patients receiving HCV treatment who developed severe anemia or who achieved SVR. The average change in CLDQ-HCV domain scores ranged from -0.33 to -0.74 for those with severe anemia and from 0.30 to 0.85 for those with SVR.[30] The exception was the worry domain, which improved approximately 0.5 points in patients who developed anemia, which the authors attributed to the fact that patients were receiving treatment. Test-retest correlations for the domain scores ranged from 0.71 to 0.98 for comparisons between paper-based and/or electronic versions of the instrument.[30]

One abstract presented data on the validation of CLDQ-HCV in 62 hepatitis C patients versus 100 healthy blood donors.[47] Hepatitis C patients received pegylated interferon with ribavirin treatment. Hepatitis C patients had a lower (worse) CLDQ-HCV overall score at baseline compared with healthy controls (5.7 ± 0.7 versus 6.2 ± 0.5, $P < 0.0001$). Lower scores were also reported at baseline for emotion and worry in hepatitis C patients (5.6 ± 0.4 and 5.7 ± 0.9) compared with healthy controls (5.9 ± 0.4 and 6.9 ± 0.2), respectively. After four weeks and 24 weeks of treatment, overall scores decreased (worsened) in hepatitis C patients (5.4 ± 0.9 and 5.7 ± 0.8), and increased after treatment discontinuation (6.3 ± 0.6). The CLDQ-HCV was able to differentiate between hepatitis C patients and healthy controls. The instrument was also sensitive to change over time.[47]

No MCID for the CLDQ-HCV instrument was identified.

Functional Assessment of Chronic Illness Therapy-Fatigue Questionnaire

The FACIT measurement system is a group of HRQL questionnaires focused on the management of chronic illness.[32] The original instrument (the Functional Assessment of Cancer Therapy [(FACT]) was developed and validated in cancer patients.[48] FACIT was later derived from FACT and validated in patients with chronic conditions such as multiple sclerosis and rheumatoid arthritis.[32] FACIT is based on a generic core questionnaire (FACT-General), which includes 27 items divided into four primary domains: physical, social/family, emotional, and functional well-being.[32] The FACIT-F is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, and low energy, as well as fatigue's impact on daily activities and function. The fatigue subscale has a seven-day recall period and includes 13 items scored using a 4-point Likert scale (with a subscale score ranging from 0 to 52).[31] 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).[31,32] Alternatively, the Trial Outcome Index score may be calculated by summing the physical well-being, functional well-being, and fatigue subscales.[32] Although no information on the validity of the 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, and the MCID in the FACIT-F ranged from 3 to 4 points in rheumatoid arthritis patients.[32,33]

Conclusion

- SF-36, a generic health assessment questionnaire, has shown good construct validity in hepatitis C patients. A mean MCID of 4.2 points (within a 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, but the generally recommended MCID from the instrument developer for the PCS and MCS is 2 to 3 points.
- Limited information was found on the validity of the WPAI questionnaire in hepatitis C; however, the MCID for the WPAI has been reported to be ≥ 7 percentage points in patients suffering from Crohn's disease.
- The CLDQ-HCV has shown good reliability and validity in hepatitis C patients. No information on the MCID of this instrument in hepatitis C could be identified.
- Although no information was found on the validity and MCID of the FACIT-F in hepatitis C, the MCID in the FACIT-F ranged from 3 to 4 points in rheumatoid arthritis patients.

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