Common Drug Review
Clinical Review Report

October 2016

Drug	Sofosbuvir/Velpatasvir (Epclusa)
Indication	• For the treatment of chronic hepatitis C virus (HCV) infection in adults without cirrhosis or with compensated cirrhosis. • In combination with ribavirin for the treatment of chronic hepatitis C virus (HCV) infection in adults with decompensated cirrhosis.
Reimbursement request	As per indication
Dosage form	Sofosbuvir/Velpatasvir is one tablet of 400 mg/100 mg taken orally
NOC date	11 July 2016
Manufacturer	Gilead Sciences Canada, Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
CI	confidence interval
CHC	chronic hepatitis C
CLDQ-HCV	HCV-specific version of the Chronic Liver Disease Questionnaire
CTP	Child–Turcotte–Pugh
CrCl	creatinine clearance
DB	double-blind
DAA	direct-acting antiviral
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
FAS	full analysis set
FDC	fixed-dose combination
GT	genotype
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HRQoL	health-related quality of life
IFN	interferon
LOCF	last observation carried forward
MCID	minimal clinically important difference
MCS	mental component summary
MELD	Model for End-Stage Liver Disease
PCS	physical component summary
PP	per-protocol
PR	pegylated interferon plus ribavirin
RBV	ribavirin
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form (36) Health Survey
SOF	sofosbuvir
SVR	sustained virologic response
VEL	velpatasvir
WDAE	withdrawal due to adverse event
WPAI	Work Productivity and Activity Impairment questionnaire

EXECUTIVE SUMMARY

Introduction

In 2013, an estimated 250,000 Canadians had chronic hepatitis C (CHC) virus infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[1] There are six major hepatitis C virus (HCV) genotypes, of which genotype 1 infections are the most common in Canada (approximately 65%).[1] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, respectively.[1] Genotype 4 is less common in Canada and accounts for fewer than 1% of HCV cases.[1] Hepatitis C most commonly affects people older than 30 years, and disproportionately men.[2] Other populations at higher risk for HCV infection include federal inmates, men who have sex with men, street-involved youth, and Aboriginal peoples.[2] Of those with chronic infection, 15% to 25% will develop progressive liver disease, end-stage liver disease, or hepatocellular carcinoma, or will require liver transplant.[3] It is expected that liver-related morbidity and mortality will increase over the coming decades, as those who are already infected age.[1,4-7] Patients have expressed the need for affordable and accessible new treatments with higher cure rates, better side effect profiles, and reduced treatment burden, particularly for those with genotypes 3 and 4 CHC.

The treatment paradigm for hepatitis C has been shifting rapidly as evidence emerges and new direct-acting antiviral (DAA) agents come onto the market. A number of interferon (IFN)-free DAA regimens have recently been approved in Canada for CHC genotypes 1 to 4, with improved tolerability, high response rates, and shorter treatment durations than the previous IFN-based treatment regimens.[8] Currently, there are no DAAs or any pegylated interferon plus ribavirin (PR)–free treatment regimen approved in Canada for these patients, except sofosbuvir (400 mg)/velpatasvir (100 mg) for the treatment of patients with HCV genotype 5 and genotype 6. Epclusa is a combination of sofosbuvir (SOF) and velpatasvir (VEL). The recommended dosage is one tablet daily of Epclusa for 12 weeks for patients without cirrhosis and patients with compensated cirrhosis, and one tablet daily of Epclusa plus weight-based ribavirin (RBV) for 12 weeks for patients with decompensated cirrhosis. The objective of this systematic review was to evaluate the beneficial and harmful effects of SOF/VEL alone or in in combination with other agents for genotypes 1, 2, 3, 4, 5, and 6 CHC.

Indication under review
• For the treatment of chronic hepatitis C virus (HCV) infection in adults without cirrhosis or with compensated cirrhosis. • In combination with ribavirin for the treatment of chronic hepatitis C virus (HCV) infection in adults with decompensated cirrhosis.
Listing criteria requested by sponsor
As per indication

Results and interpretation

Included studies

A total of four pivotal phase 3 clinical trials were included in this review (ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4). All trials were randomized and multi-centre. ASTRAL-1 was double blind, while ASTRAL-2, ASTRAL-3, and ASTRAL-4 were open label. ASTRAL-1 (N = 741) assessed the efficacy and safety of SOF/VEL for 12 weeks compared with placebo among treatment-naive and previously treated patients with chronic genotype 1, 2, 4, 5, or 6 HCV infection, including those with compensated cirrhosis.

ASTRAL-2 (N = 269) assessed the efficacy and safety of 12 weeks of the SOF/VEL treatment compared with 12 weeks of SOF + RBV treatment in treatment-naive and previously treated patients with chronic genotype 2 HCV infection, including those with compensated cirrhosis. ASTRAL-3 (N = 558) assessed the efficacy and safety of 12 weeks of the SOF/VEL treatment compared with 24 weeks of SOF + RBV treatment in treatment-naive and previously treated patients with chronic genotype 3 HCV infection, including those with compensated cirrhosis. ASTRAL-4 (N = 268) assessed the efficacy and safety of SOF/VEL + RBV for 12 weeks in treatment-naive and previously treated patients with chronic genotypes 1 through 6 who had decompensated cirrhosis (classified as Child–Turcotte–Pugh [CTP] class B).

The primary outcome in the included trials was the proportion of patients achieving sustained virologic response at 12 weeks (SVR12). Other outcomes included relapse rate and health-related quality of life (HRQoL). The main limitation of the ASTRAL-1 trial was the lack of an active treatment comparator arm consisting of an existing treatment regimen for CHC genotype 1, 2, 4, 5, or 6 infection. Similarly, in ASTRAL-4, the lack of an active treatment comparator arm consisting of an existing treatment regimen for CHC was also the main limitation. All included trials except ASTRAL-1 were open-label trials; therefore, awareness of the treatment allocation might have influenced subjective measures such as HRQoL and reporting of adverse events (AEs). The primary outcome in ASTRAL-1 compared SVR12 with a benchmark performance goal of 85%. The rationale for this performance goal was not provided. The ASTRAL-4 trial compared SVR12 rate versus a spontaneous rate of 1%. However, currently there are other treatments indicated for patients with HCV with compensated and decompensated cirrhosis, which could have been selected as valid comparators. Despite the scientific limitations associated with the current study designs, they were considered adequate by Health Canada and the FDA to grant regulatory approval. In the ASTRAL-4 trial, there were limited data available in patients with genotypes 2 or 4 HCV, and no patients with genotypes 5 or 6 HCV were enrolled in the SOF/VEL + RBV treatment arm. Hence, there is uncertainty regarding the SVR for these genotypes.

Efficacy

In the ASTRAL-1 study, which included treatment-naive and previously treated patients with chronic genotype 1, 2, 4, 5, or 6 HCV infection, including those with compensated cirrhosis, the Health Canada–approved regimen of SOF/VEL for 12 weeks was associated with high rates of successful treatment. The SVR12 rate with SOF/VEL was 99.0% (95% confidence interval [CI], 97.9% to 99.6%) which occurred in 618 of 624 patients. This rate was statistically superior relative to the pre-specified performance goal of 85% ($P < 0.001$). Again, no direct comparison was made to the placebo arm. In the ASTRAL-2 study, which included treatment-naive and previously treated patients with chronic genotype 2 HCV infection, including those with compensated cirrhosis, SOF/VEL for 12 weeks was also associated with high rates of successful treatment: SVR12: 99.3% (95% CI, 95.9% to 100%) in 133 of 134 patients, while in the SOF + RBV for 12 weeks treatment group, SVR12: 93.9% (95% CI, 88.4% to 97.3%) in 124 of 132 patients. The 12-week regimen of SOF/VEL was statistically noninferior to SOF + RBV for 12 weeks (SVR difference: 5.2%; 95% CI, 0.2%, 10.3%), the primary end point of the study. Treatment with SOF/VEL for 12 weeks was shown to be statistically superior to SOF + RBV for 12 weeks, as demonstrated by the *P* value of 0.018. In ASTRAL-3, which included treatment-naive and previously treated patients with chronic genotype 3 HCV infection, including those with compensated cirrhosis, the Health Canada–approved regimen of SOF/VEL for 12 weeks was associated with high rates of successful treatment: SVR12: 95.3% (95% CI, 92.1% to 97.5%) in 264 of 277 patients, while in the SOF + RBV for 24 weeks treatment group, SVR12 was 80.4% (95% CI, 75.2% to 84.9%) in 221 of 275 patients. The strata-adjusted difference (95% CI) in the proportions was 14.8% (95% CI, 9.6% to 20.0%), demonstrating superiority of treatment with SOF/VEL for 12 weeks over SOF + RBV for 24 weeks for SVR12. In the ASTRAL-4 study, which included patients with decompensated cirrhosis, the SVR12 rate for the SOF/VEL + RBV for 12 weeks treatment

group was 94.3% (95% CI, 87.1% to 98.1%) in 82 of 87 patients. The SOF/VEL + RBV for 12 weeks treatment group met the primary efficacy end points with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%.

In ASTRAL-1, the SVR12 rates were 98.6% (72 of 73) and 99.1% (109 of 110) in cirrhotic and treatment-experienced genotype 1 HCV-infected patients, respectively. Among genotype 1 HCV-infected patients treated with a DAA + PR, the SVR12 rate was 100% (48 of 48). The SVR12 rate among genotype 2 HCV-infected patients in the SOF/VEL for 12 weeks treatment group was 100%. Approximately 24% and 10% of genotype 2 HCV-infected patients had cirrhosis and prior treatment experience, respectively. The SVR12 rate among genotype 4 HCV-infected patients in the SOF/VEL for 12 weeks treatment group was 100%. Fifty-two of 116 patients (44.8%) with genotype 4 HCV infection had prior treatment failure and 27 patients (23.3%) had cirrhosis. The SVR12 rate among genotype 5 HCV-infected patients was 97.1%. Eleven of 35 patients (31%) had prior treatment failure and five of 35 patients (14.3%) had cirrhosis. The SVR12 rate among genotype 6 HCV-infected patients was 100%. [redacted] There were two virologic failures among 624 patients treated with SOF/VEL; both had genotype 1 HCV infection and both relapsed by post-treatment week 4. There were no virologic failures among the 104 genotype 2, 116 genotype 4, 35 genotype 5, and 41 genotype 6 HCV-infected patients treated with SOF/VEL. [redacted] Baseline nonstructural protein 5A (NS5A) or NS5B resistance-associated variants (RAVs) had no impact on SVR12, with high SVR12 across all HCV genotypes and subtypes regardless of the presence of RAVs.

In the ASTRAL-2 study, no virologic failures were observed with SOF/VEL for 12 weeks, compared with six virologic failures (4.5%) with SOF + RBV for 12 weeks. Treatment with SOF/VEL for 12 weeks resulted in high SVR12 rates, with no virologic failures in patients with genotype 2 HCV infection, irrespective of treatment status, cirrhosis, and presence of baseline NS5A RAVs. The SVR rates with SOF/VEL for 12 weeks in patients with cirrhosis, prior treatment failure, or baseline RAVs were 100%.

In the ASTRAL-3 study, among patients who were treated with SOF/VEL for 12 weeks, prior treatment experience (SVR12: 90.1% ; 64 of 71 patients) and cirrhosis (SVR12: 91.3% SVR; 73 of 80 patients) appeared to have a moderate negative impact on treatment responses. In the patient group with both cirrhosis and prior HCV treatment experience, the SVR12 rate was 89% (33 of 37 patients). The SVR12 rate for patients without cirrhosis was 97.0% (191 of 197 patients) and 97.1% (200 of 206 patients) among treatment-naive patients. The SVR12 rate was 89.1% (57 of 64 patients) in those who had received a prior PR regimen and 85.0% (17 of 20 patients) in those who were non-responders to prior HCV treatment. In the SOF + RBV for 24 weeks treatment group, patients with cirrhosis had considerably lower SVR12 rates (66.3%; 55 of 83) than patients without cirrhosis (87.2%; 163 of 187), and patients with prior treatment experience had considerably lower SVR12 rates (63.4%; 45 of 71) than treatment-naive patients (86.3%; 176 of 204). [redacted] There was a lower SVR12 rate in SOF/VEL-treated patients with baseline NS5A RAVs compared with patients without NS5A RAVs (88% versus 97%, respectively). In the SOF/VEL for 12 weeks treatment group, the Y93H was detected in 25 ([redacted]%) of patients with an SVR12 rate of 84% (21/25). A total of 10 patients in the SOF/VEL for 12 weeks treatment group relapsed, and one patient was reinfected. All 10 patients had the NS5A RAV Y93H detected at relapse time points.

In the ASTRAL-4 study, among patients with genotype 1 HCV infection, the SVR12 rate was 95.6% (65 of 68); among patients with genotype 3 HCV infection, the SVR12 rate was 84.6% (11 of 13). All patients with genotype 2 or 4 HCV infection achieved SVR12. Treatment with SOF/VEL + RBV for 12 weeks resulted in high SVR12 rates irrespective of genotype, prior treatment history, or baseline HCV ribonucleic acid (RNA). However, the number of patients included was limited (four patients with genotype 2; two patients with genotype 4; and no patients with genotype 5 or 6); hence, the generalizability of the results for genotypes 2, 4, 5, or 6 is questionable. The presence of pre-treatment NS5A RAVs did not affect treatment outcome, while in genotype 1 HCV-infected patients, the SVR12 rates in patients with or without pre-treatment RAVs were similar in the SOF/VEL + RBV for 12 weeks treatment group. All patients with genotype 2 or 4 HCV infection achieved SVR12 irrespective of the presence of pre-treatment RAVs. Interpretation of the analyses of the impact of NS5A RAVs on treatment outcome in patients with genotype 3 HCV infection is limited by the small number of patients with NS5A RAVs. In the SOF/VEL + RBV for 12 weeks treatment group, three patients (one with genotype 1a and two with genotype 3a) experienced virologic failure. One patient with genotype 1a HCV infection had no NS5A or NS5B RAVs at failure. One patient with genotype 3a HCV infection had Y93H emerge at failure. Another patient with genotype 3a HCV infection had HCV with Y93H at pre-treatment and relapse, and also developed low levels of NS5B N142T+E237G at failure.

ASTRAL-4 assessed improvement in Model for End-Stage Liver Disease (MELD) and CTP scores. Improvements in hepatic function, as indicated by reductions in CTP and MELD scores, were seen in a high proportion of patients, where 41 of 81 patients (50.6%) had improvement in MELD score and 33 patients (40.7%) had an improvement in CTP score. Twelve patients (14.8%) had no change in their MELD score, and 40 patients (49.4%) had no change in their CTP score. Improvements in MELD score were largely due to improvements in total bilirubin levels. Improvements in CTP score were largely due to improvements in albumin and bilirubin levels. Ten patients had MELD scores of 15 or more at baseline; these patients were most likely to have improvements in MELD, where [redacted]% ([redacted] of 10 patients) had improvement in MELD score; however, this subgroup was small. [redacted] Whether these changes in MELD and CTP scores will persist is unknown.

Patient group input emphasized the impact that CHC infection has on patients' quality of life. HRQoL was measured using the Short Form (36) Health Survey (SF-36), and the HCV-specific version of the Chronic Liver Disease Questionnaire (CLDQ-HCV) in all four trials. [redacted]

[redacted]
unlike what is typically seen with HRQoL scores from other DAA-based regimens that include PR.[9] Finally, it is worth noting that patient-reported outcomes for all four studies should be interpreted with caution, as multiple end points were tested, and the study was not powered to test these exploratory end points.

Despite the absence of direct comparative trials of SOF/VEL with other treatments for CHC infection genotypes 1 and 4 and patients with decompensated cirrhosis, no indirect treatment comparisons were submitted by the manufacturer or identified in the literature.

Harms

Adverse events (AEs) were frequent across all treatment groups in the included trials, ranging from [redacted] to [redacted] while on SOF/VEL for 12 weeks, 90.8% among those who received SOF/VEL + RBV for 12 weeks, while for those who received SOF + RBV for 12 weeks and SOF + RBV for 24 weeks, it was 76.5%, and 94.5%, respectively, and for those who received placebo, the rate of adverse events (AEs) was 76.7%. In ASTRAL-1, SOF/VEL for 12 weeks was generally well tolerated, with a similar safety profile in the active and placebo treatment groups. The incidence of serious adverse events (SAEs) in the SOF/VEL-treated patients ranged from [redacted] and all SAEs were assessed by investigators as not related to study drug. Discontinuations for AEs were uncommon. The most common AEs were headache, fatigue, and nasopharyngitis in patients who received SOF/VEL for 12 weeks, while in those who received placebo for 12 weeks, it was headache, fatigue, and nausea. In the ASTRAL-2 trial, treatment with SOF/VEL for 12 weeks was well tolerated in this study and compared favourably to SOF + RBV for 12 weeks. [redacted] In ASTRAL-3, treatment with SOF/VEL for 12 weeks was well tolerated in this study and compared favourably with SOF + RBV for 24 weeks. [redacted] In ASTRAL-4, treatment with SOF/VEL+ RBV was safe and well tolerated in this patient population with decompensated liver disease. A high percentage of patients in the SOF/VEL + RBV for 12 weeks treatment group experienced any AE (90.8%), primarily consistent with RBV-related toxicity. The most common AEs, occurring in more than 10% of patients, were fatigue, nausea, and anemia. The relative safety of SOF/VEL compared with other available HCV therapies except for SOF + RBV is inconclusive without a direct or indirect comparative evaluation.

Conclusions

Based on data from four pivotal phase 3 randomized clinical trials (one double-blinded placebo-controlled trial that also compared SVR12 versus a performance goal of 85%, two open-label trials that had active comparators, and one uncontrolled, open-label trial), SOF/VEL was associated with high rates of SVR12 in patients with genotype 1, 2, 3, 4, 5, and 6 CHC infection. High rates of SVR12 were observed across several subgroups of interest: In treatment-naive and previously treated patients, including those with compensated cirrhosis, as well as patients with chronic genotype 1, 2, 3, or 4 HCV infection who had decompensated cirrhosis. The SVR12 rate for SOF/VEL in ASTRAL-1 was statistically superior relative to the pre-specified performance goal of 85%. In ASTRAL-2, SOF/VEL for 12 weeks was shown to be statistically superior to SOF + RBV for 12 weeks in patients with genotype 2, and in the ASTRAL 3 study, SOF/VEL for 12 weeks was shown to be statistically superior to SOF + RBV for 24 weeks in patients with genotype 3. In decompensated cirrhosis (ASTRAL-4), the SVR12 rate for the SOF/VEL + RBV for 12 weeks treatment group was 94.3%, meeting the primary efficacy end points with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%. The data were limited for some populations in ASTRAL-4; specifically, patients with CHC genotype 2 or 4, and no patients with genotype 5 or 6 were enrolled. [redacted] SAEs and withdrawals due to AEs were very limited, indicating good tolerability of the evaluated medication. Characteristic AEs associated with pegylated IFN appeared to occur less frequently among patients treated with SOF/VEL. However, the relative efficacy and safety of SOF/VEL compared with more recent IFN-free HCV therapies is uncertain, due to the absence of direct or indirect comparative evaluations.

TABLE 1: SUMMARY OF RESULTS

Outcome	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 weeks (n = 624)	PBO 12 weeks (n = 116)	SOF/VEL for 12 weeks (n = 134)	SOF + RBV for 12 weeks (n = 132)	SOF/VEL for 12 weeks (n = 277)	SOF + RBV for 24 weeks (n = 275)	SOF/VEL + RBV for 12 weeks (n = 87)
SVR12 (Full Analysis Set)							
N (%) 95% CI	618 (99) 97.9 to 99.6	0	133 (99.3) 95.9 to 100.0	124 (93.9) 88.4 to 97.3	264 (95.3) 92.1 to 97.5	221 (80.4) 75.2 to 84.9	82/87 (94.3) 87.1 to 98.1
Difference (95% CI)			5.2 (0.2 to 10.3)		14.8 (9.6 to 20.0)		
P value			0.018		< 0.001		
SVR12 by HCV Genotype, n (%)							
Genotype 1	323 (98.5)						65 (95.6)
Genotype 1a	206 (98.1)						51 (94.4)
Genotype 1b	117 (99.2)						14 (100.0)
Genotype 2	104 (100.0)		133 (99.3)	124 (93.9)			4 (100.0)
Genotype 3	NA				264 (95.3)	221 (80.4)	11 (84.6)
Genotype 4	116 (100.0)						2 (100.0)
Genotype 5	34 (97.1)						NA
Genotype 6	41 (100.0)						NA
MELD Scores Between Baseline and Post-Treatment Week 12, n (%)							
Decrease (improvement)							41/81 (50.6)
No change							12/81 (14.8)
Increase (worsening)							28/81 (34.6)
No assessment							1
CTP Scores Between Baseline and Post-Treatment Week 12, n (%)							
Decrease (improvement)							33/81 (40.7)
No change							40/81 (49.4)
Increase (worsening)							8/81 (9.9)
No assessment							1
[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 weeks (n = 624)	PBO 12 weeks (n = 116)	SOF/VEL for 12 weeks (n = 134)	SOF + RBV for 12 weeks (n = 132)	SOF/VEL for 12 weeks (n = 277)	SOF + RBV for 24 weeks (n = 275)	SOF/VEL + RBV for 12 weeks (n = 87)
[redacted]							
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Adverse Events							
Any AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	79 (90.8)
SAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14 (16.1)
Death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3 (3.4)
AE leading to discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (4.6)

AE = adverse event; CI = confidence interval; CLDQ-HCV = Chronic Liver Disease Questionnaire–Hepatitis C version; EOT = end of treatment; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; HCV = hepatitis C virus; MELD = Model for End-Stage Liver Disease; NA = not applicable; PBO = placebo; RBV = ribavirin; SAE = serious adverse event; SD = standard deviation; SF-36 = Short Form (36) Health Survey; SOF = sofosbuvir; VEL = velpatasvir.

1. INTRODUCTION

1.1 Disease prevalence and incidence

Hepatitis C infection 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 hepatitis C virus (HCV)infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[1] A total of 11,357 cases of HCV were reported in Canada in 2009, mostly due to injection drug use.[2] Hepatitis C most commonly affects people older than 30 years, and disproportionately men, although the gender gap is narrowing.[2] Other populations at higher risk for HCV infection include federal inmates, men who have sex with men, street-involved youth, and Aboriginal peoples.[2] There are six major HCV genotypes, of which genotype 1 infections are the most common in Canada (65%).[1] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, respectively.[1] Genotypes 4, 5, and 6 are less common in Canada and account for fewer than 1% of HCV cases.[1]

Of those infected, approximately 25% clear infection spontaneously (range 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 hepatocellular carcinoma (HCC), or will require liver transplant.[3] Male gender, alcohol use, HIV coinfection, obesity, and increasing age are associated with an increased risk of liver disease progression.[3,13] While the incidence of HCV infection appears to be stable or declining in North America and Canada, it is expected that liver-related morbidity and mortality will continue to increase over the coming decades, as those who are already infected age.[1,4-7]

1.2 Standards of therapy

The treatment paradigm for chronic hepatitis C (CHC) infection continues to evolve rapidly. Prior to 2011, pegylated interferon plus ribavirin (PR) was the gold standard therapy for patients with CHC infection. Approximately half of patients infected with genotype 1 HCV could expect to achieve sustained virologic response (SVR) with a 48-week course of PR therapy.[8] In recent years, greater understanding of the HCV replication cycle has resulted in the development of direct-acting antiviral (DAA) drugs that target several types of nonstructural proteins used to support viral replication (Table 3). These regimens resulted in a further advance in SVR rates compared with PR regimens that did not include a DAA. The first DAAs approved in Canada (boceprevir, telaprevir, simeprevir, and sofosbuvir) were used in combination with PR in patients with genotype 1 CHC (Table 5). A major limitation to PR-based treatment regimens has been their poor tolerability. A number of interferon-free DAA regimens have now been approved in Canada for genotypes 1, 2, 3 and 4 CHC, with improved tolerability, high response rates, and shorter treatment durations (Table 6).[8] The treatment paradigm for hepatitis C has been shifting rapidly as new evidence emerges. Use of the protease inhibitors, boceprevir and telaprevir, has been replaced by newer DAA regimens; telaprevir is no longer marketed in Canada, and boceprevir will soon be discontinued as well.[8] The recommendation from the CADTH Canadian Drug Expert Committee (CDEC) on the CADTH Therapeutic Review titled *Drugs for Chronic Hepatitis C Infection* was that ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin were preferred regimens for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status; sofosbuvir/ribavirin for 12 weeks for patients with CHC genotype 2 infection, regardless of cirrhosis status; daclatasvir/sofosbuvir for 12 weeks for patients with CHC genotype 3 infection, without cirrhosis; sofosbuvir/ribavirin for 24 weeks for patients with CHC genotype 3 infection, with cirrhosis; and sofosbuvir + PR for 12 weeks in treatment-naive patients with CHC genotype 4 infection who are non-cirrhotic, and CDEC considered that there was insufficient

evidence to make a recommendation in genotype 4 treatment-experienced patients, or patients with cirrhosis regardless of treatment experience. CDEC considered that there was insufficient evidence to make a recommendation for patients with CHC genotype 5 or 6 infection.[14]

The Infectious Diseases Society of America and American Association for the Study of Liver Diseases (AASLD)[15] have included sofosbuvir/velpatasvir (SOF/VEL) in their latest set of guidelines. They have recommended 12 weeks of SOF/VEL for treatment-naive and PR-experienced patients with CHC genotype 1, 2, 3, 4, 5, and 6 infection, regardless of cirrhosis status. There are also specific recommendations for subgroups of the CHC population. SOF/VEL is a recommended regimen for genotype 1 treatment-experienced patients who had been previously treated with a HCV protease inhibitor (telaprevir, boceprevir, or simeprevir) plus PR-experienced patients. SOF/VEL plus weight-based ribavirin (RBV) for 12 weeks is a recommended regimen for patients with HCV genotype 2 or genotype 3 infection, regardless of cirrhosis status, in whom prior treatment with sofosbuvir and ribavirin has failed. For patients with HCV genotype 1 or 4 infection who have decompensated cirrhosis, SOF/VEL plus weight-based RBV for 12 weeks is a recommended regimen, and SOF/VEL for 24 weeks is a recommended regimen for those who are ribavirin ineligible. Patients with HCV genotype 1 or 4 infection who have decompensated cirrhosis and in whom prior SOF- or NS5A-based treatment has failed, SOF/VEL plus weight-based RBV for 24 weeks is a recommended regimen. SOF/VEL is also recommended in combination with weight-based RBV for patients with HCV genotype 2 or 3 infection who have decompensated cirrhosis and who may or may not be candidates for liver transplantation, including those with HCC.[15] SOF/VEL was not the only recommended regimen by AASLD, which recommends several other regimens for some subgroups or genotypes.

For patients with HCV genotype 1, real-world study data have consistently shown results comparable to those reported in the phase 3 clinical trials.[16-18] For patients with HCV genotype 2, although the SOF + RBV regimen has demonstrated high rates of SVR12 in both clinical studies and the real-world setting, the hematologic, dermatologic, and neuropsychiatric side effects associated with RBV can cause a significant burden to patients.[19] Many patients with hemoglobinopathies, cardiovascular disease, and chronic pulmonary disease cannot be treated with RBV-containing regimens due to the hemolysis caused by RBV.[20]

For patients with HCV genotype 3, real-world data for genotype 3 cirrhotic patients treated with SOF + RBV for 24 weeks has demonstrated inconsistent SVR12 rates compared with phase 3 clinical trials.[21-23] In the TARGET 2.0 and TRIO studies, 51% and 80% achieved SVR12, versus 60% in the phase 3 VALENCE study. Recently, Daklinza (daclatasvir) and Zepatier (elbasvir/grazoprevir with or without [±] RBV) have been approved for co-administration with sofosbuvir for the treatment of genotype 3 patients.[24,25] Daklinza currently has a conditional approval (Notice of Compliance With Conditions [NOC/c]) and requires 24 weeks' treatment duration in cirrhotic patients.[24] Zepatier is approved in treatment-naive patients only.[25]

For patients with HCV genotype 4, two interferon (IFN)-free regimens have recently been approved by Health Canada for the treatment of genotype 4 patients: Technivie (ombitasvir/paritaprevir/ritonavir + RBV) and Zepatier (elbasvir/grazoprevir ± RBV). However, Technivie includes RBV and is not approved in cirrhotic patients,[26] and Zepatier requires 16 weeks' treatment duration with RBV in patients with previous on-treatment virologic failure, and is also contraindicated in decompensated cirrhotic patients.[25]

There have been very few to no advances in the treatment of patients with HCV genotype 5 and genotype 6. Due to the limited number of patients who are infected with these genotypes, clinical trial data in these patients are very limited.[8] Currently, there are no DAAs or any PR-free treatment regimens approved in Canada for these patients, other than SOF/VEL.

There are limited options for some specific subgroups of patients with CHC. There are few treatment options available for HCV-infected patients with decompensated liver disease, where SOF/VEL is the only regimen recommended for the treatment of all HCV genotypes in patients with decompensated cirrhosis.[27] Daclatasvir currently has an indication to use in combination with other drugs for the treatment of CHC in adult patients with HCV genotypes 1, 2, or 3, including patients with HIV-1 coinfection, patients with compensated or decompensated cirrhosis, and patients with HCV recurrence after liver transplantation.[24] Ledipasvir currently has an indication for the treatment of genotype 1 CHC infection in adult patients with decompensated cirrhosis (Child–Pugh class B or C) in combination with SOF and RBV.[28]

1.3 Drug

Epclusa is a fixed-dose combination of SOF and VEL. SOF/VEL is formulated in a single tablet; the tablet is composed of 400 mg sofosbuvir, and 100 mg velpatasvir. The recommended dosage is one tablet daily of Epclusa for 12 weeks for patients without cirrhosis and patients with compensated cirrhosis, and one tablet daily of Epclusa plus weight-based RBV for 12 weeks for patients with decompensated cirrhosis (Table 2).[27]

Indication under review
• For the treatment of chronic hepatitis C virus (HCV) infection in adults without cirrhosis or with compensated cirrhosis. • In combination with ribavirin for the treatment of chronic hepatitis C virus (HCV) infection in adults with decompensated cirrhosis.
Listing criteria requested by sponsor
As per indication

TABLE 2: DOSING REGIMEN FOR EPCLUSA

Patient Population	Treatment Composition	Dosage	Duration
All HCV genotypes in patients without cirrhosis and patients with compensated cirrhosis	sofosbuvir/velpatasvir	400 mg/100 mg once daily	12 weeks
All HCV genotypes in patients with decompensated cirrhosis	sofosbuvir/velpatasvir + ribavirin	400 mg/100 mg once daily < 75 kg = 1,000 mg per day; ≥ 75 kg = 1,200 mg per day	

HCV = hepatitis C virus.
Source: Epclusa product monograph.[27]

TABLE 3: KEY CHARACTERISTICS OF DIRECT-ACTING ANTIVIRALS APPROVED FOR USE IN CANADA

Drug	Mechanism of Action	Health Canada Indication	Serious Side Effects / Safety Issues
Simeprevir	HCV NS3/4A protease inhibitor: The protease is essential for viral replication.	Treatment of CHC genotype 1 or genotype 4 infection, in combination with PR in adults with compensated liver disease, including cirrhosis *Conditional marketing authorization:* Treatment of genotype 1 CHC use in combination with sofosbuvir in adults with compensated liver disease including cirrhosis	Rash, pruritus, nausea
Sofosbuvir	HCV NS5B polymerase inhibitor. The NS5B polymerase is an RNA polymerase that is critical for the viral replication cycle.	Treatment of genotype 1 CHC infection in adults in combination with ledipasvir Treatment of all HCV genotypes in adult patients without cirrhosis and patients with compensated cirrhosis in combination with velpatasvir Treatment of all HCV genotypes in adult patients with decompensated cirrhosis in combination with velpatasvir and ribavirin 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, insomnia
Ledipasvir	HCV NS5A inhibitor. The NS5A protein is an essential component of HCV replicase, even though no known enzymatic function has been associated with it.	Treatment of genotype 1 CHC infection in adults in combination with sofosbuvir Treatment of genotype 1 CHC infection in adult liver transplant recipients without cirrhosis, or with compensated cirrhosis in combination with sofosbuvir and ribavirin Treatment of genotype 1 CHC infection in adult patients with decompensated cirrhosis (Child–Pugh class B or C) in combination with sofosbuvir and ribavirin	Fatigue, headache

Drug	Mechanism of Action	Health Canada Indication	Serious Side Effects / Safety Issues
Ombitasvir/ paritaprevir/ ritonavir and dasabuvir ± ribavirin	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, which 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 CHC infection including those with compensated cirrhosis	Fatigue, headache, nausea, pruritus, insomnia
Ombitasvir/ paritaprevir/ ritonavir ± ribavirin	Ombitasvir: HCV NS5A inhibitor that inhibits viral replication. Paritaprevir: HCV NS3/4A protease inhibitor that inhibits viral replication. Ritonavir: Pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir. It is not active against HCV.	Treatment of CHC genotype 4 infection in adults without cirrhosis	Fatigue, headache, nausea, pruritus, insomnia
Daclatasvir	Inhibitor of the NS5A replication complex.	In combination with other drugs for the treatment of CHC in adult patients with HCV genotype 1 or 2 infection and compensated liver disease, including cirrhosis In combination with other drugs for the treatment of CHC in adult patients with HCV genotypes 1, 2, or 3, including patients with HIV-1 coinfection, patients with compensated or decompensated cirrhosis, and patients with HCV recurrence after liver transplantation *Conditional marketing authorization:* In combination with other drugs for the treatment of CHC in adult patients with HCV genotype 3 infection and compensated liver disease, including cirrhosis Daclatasvir has been issued marketing authorization with conditions, pending the results of a trial to	Headache, fatigue

Drug	Mechanism of Action	Health Canada Indication	Serious Side Effects / Safety Issues
		verify its clinical benefit.	
Elbasvir/ grazoprevir	Elbasvir is an HCV NS5A inhibitor. Grazoprevir is an HCV NS3/4A protease inhibitor.	Alone or in combination with ribavirin for the treatment of CHC genotypes 1 or 4 infection in adults In combination with sofosbuvir for the treatment of CHC genotype 3 infection in treatment-naive adult patients	Nausea, headache, fatigue
Asunaprevir	HCV NS3/4A serine protease inhibitor that inhibits viral replication.	In combination with other drugs for the treatment of CHC in adult patients with HCV genotypes 1 or 4 and compensated liver disease, including cirrhosis	Headache, fatigue
Velpatasvir	Velpatasvir is an HCV inhibitor targeting the HCV NS5A protein.	Treatment of all HCV genotypes in adult patients without cirrhosis and patients with compensated cirrhosis in combination with sofosbuvir Treatment of all HCV genotypes in adult patients with decompensated cirrhosis in combination with sofosbuvir and ribavirin	Headache, fatigue

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; NS3/4A = nonstructural protein 3/4A; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; RNA = ribonucleic acid.
Source: Product monographs.[24-32]

TABLE 4: KEY CHARACTERISTICS OF PEGYLATED INTERFERON PLUS RIBAVIRIN REGIMENS

Drug	Mechanism of Action	Health Canada Indication
Peginterferon alfa-2a, Peginterferon alfa-2a plus ribavirin	Interferons bind to specific receptors on the cell surface, initiating a complex intracellular signalling pathway and rapid activation of gene transcription. Interferon-stimulated genes modulate many biological effects, including the inhibition of viral replication in infected cells, inhibition of cell proliferation, and immunomodulation. The mechanism of action of ribavirin is not known	For the treatment of CHC in adult patients without cirrhosis or with compensated cirrhosis, including HCV/HIV coinfected patients with stable HIV disease with or without antiretroviral therapy
Peginterferon alfa-2b plus ribavirin		Treatment of adult patients (18 years or older) with CHC who have compensated liver disease and are positive for HCV RNA, including patients who have not received previous treatment or who failed prior treatment with interferon alfa (pegylated or non-pegylated) and ribavirin combination therapy

CHC = chronic hepatitis C; HCV = hepatitis C virus; RNA = ribonucleic acid.
Source: Product monographs.[20,33,34]

TABLE 5: DOSING REGIMENS FOR DIRECT-ACTING ANTIVIRAL AGENTS USED IN COMBINATION WITH PEGYLATED INTERFERON PLUS RIBAVIRIN

HCV	Simeprevir	Sofosbuvir	Daclatasvir/Asunaprevir
Genotype 1	Simeprevir 150 mg capsule once daily with PR **Treatment-naive:** Triple therapy for 12 weeks, followed by PR for additional 12 or 36 weeks based on RGT **Treatment-experienced:** Triple therapy for 12 weeks, plus PR for additional 12 or 36 weeks based on RGT (prior-relapsers), or for an additional 36 weeks (prior partial and null responders) **Cirrhotic patients**: As per above; no special dosing	Sofosbuvir 400 mg tablet, once daily with PR for 12 weeks	Daclatasvir 60 mg tablet daily plus asunaprevir 100 mg twice daily with PR for 24 weeks (treatment-naive or treatment-experienced, with or without compensated cirrhosis) [a]
Genotype 4	Similar to genotype 1 dosing	Similar to genotype 1 dosing	Similar to genotype 1 dosing

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy.
[a] Daclatasvir dose should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A4. Co-administration with strong or moderate CYP3A4 inhibitors is contraindicated with regimens that include asunaprevir. The dose of daclatasvir should be increased to 90 mg once daily (three 30 mg tablets or one 60 mg and one 30 mg tablet) when co-administered with moderate inducers of CYP3A4. Co-administration with moderate or strong CYP3A4 inducers is contraindicated with regimens that include asunaprevir.
Source: Product monographs.[29,30,32]

TABLE 6: RECOMMENDED DOSING FOR INTERFERON-FREE DIRECT-ACTING ANTIVIRAL REGIMENS

Treatment Regimen	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
Simeprevir/ Sofosbuvir	Simeprevir 150 mg capsule once daily with sofosbuvir 400 mg tablet, once daily for 12 weeks TN, prior relapse patients and prior nonresponder patients (including partial and null responders) with or without cirrhosis, who are not coinfected with HIV					
Sofosbuvir/ Ribavirin	Sofosbuvir 400 mg once daily in combination with ribavirin for 24 weeks can be considered as a therapeutic option for TN and non-cirrhotic TE CHC patients with genotype 1 infection who are ineligible to receive an interferon-based regimen	Sofosbuvir 400 mg tablet once daily in combination with ribavirin for 12 weeks	Sofosbuvir 400 mg tablet once daily in combination with ribavirin for 24 weeks			

Treatment Regimen	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
Sofosbuvir/ Ledipasvir	Sofosbuvir 400 mg fixed-dose combination tablet with 90 mg ledipasvir once daily for 12 weeks (24 weeks for TE patients with cirrhosis; 8 weeks can be considered for TN patients with HCV RNA > 6 million IU/mL) Sofosbuvir 400 mg fixed-dose combination tablet with 90 mg ledipasvir once daily plus ribavirin for 12 weeks for liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child–Pugh class A) or patients with decompensated cirrhosis (Child–Pugh class B or C)					
Ombitasvir/ Paritaprevir / Ritonavir and Dasabuvir	Two ombitasvir 12.5 mg / paritaprevir 75 mg / ritonavir 50 mg fixed-dose combination tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) **Genotype 1b, without cirrhosis** 12-week treatment duration **Genotype 1a, without cirrhosis** 12-week treatment duration, combined with ribavirin **Genotype 1a and 1b, with cirrhosis** 12-week treatment duration, combined with ribavirin (24-week treatment duration recommended for genotype 1a infection with cirrhosis who have had a previous null response to PR).]					
Ombitasvir/ Paritaprevir / Ritonavir				**TN or PR-TE without cirrhosis** Two ombitasvir 12.5 mg / paritaprevir 75 mg / ritonavir 50 mg fixed-dose combination tablets taken		

Treatment Regimen	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
				once daily (in the morning) for 12 weeks combined with ribavirin. Ombitasvir/paritaprevir/ritonavir administered without ribavirin for 12 weeks may be considered for TN patients who cannot take or tolerate ribavirin.		
Elbasvir / grazoprevir	One elbasvir 50 mg/grazoprevir 100 mg fixed-dose combination tablet once daily **TN, PR-TE Relapsers, or PI/PR-TE Relapsers** 12 weeks (8 weeks may be considered in TN genotype 1b patients without significant fibrosis or cirrhosis) **PR-TE or PI/PR-TE On-Treatment Virologic Failures** 12 weeks for genotype 1b (PR-TE or PI/PR-TE) Combined with ribavirin for 16 weeks for genotype 1a (PR-TE or PI/PR-TE)		One elbasvir 50 mg/grazoprevir 100 mg fixed-dose combination tablet once daily **TN** In combination with sofosbuvir 400 mg for 12 weeks	One elbasvir 50 mg / grazoprevir 100 mg fixed-dose combination tablet once daily **TN or PR-TE Relapsers** 12 weeks **PR-TE** Combined with ribavirin for 16 weeks		
Daclatasvir / Sofosbuvir	Daclatasvir 60 mg tablet daily plus sofosbuvir 400 mg tablet daily (TN, or TE)[a] **Without cirrhosis** 12 weeks **With compensated cirrhosis, decompensated cirrhosis, or post-liver transplant HCV** Combined with ribavirin for 12 weeks	Similar to genotype 1 dosing	Similar to genotype 1 dosing			
Daclatasvir / Asunaprevir	**Genotype 1b** Daclatasvir 60 mg tablet daily plus asunaprevir 100 mg twice daily for 24 weeks (TN or TE, with or without compensated cirrhosis) [a]					
Sofosbuvir / velpatasvir	Sofosbuvir 400 mg fixed-dose combination tablet with 100 mg velpatasvir once daily for 12	Similar to genotype 1	Similar to genotype 1	Similar to genotype 1 dosing	Similar to genotype 1	Similar to genotype

Treatment Regimen	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
	weeks in patients without cirrhosis and patients with compensated cirrhosis Sofosbuvir 400 mg fixed-dose combination tablet with 100 mg velpatasvir once daily plus ribavirin for 12 weeks in patients with decompensated cirrhosis	dosing	dosing		dosing	1 dosing

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy; TE = treatment-experienced; TN = treatment-naive.

[a] Daclatasvir dose should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A4. Co-administration with strong or moderate CYP3A4 inhibitors is contraindicated with regimens that include asunaprevir. The dose of daclatasvir should be increased to 90 mg once daily (three 30 mg tablets or one 60 mg and one 30 mg tablet) when co-administered with moderate inducers of CYP3A4. Co-administration with moderate or strong CYP3A4 inducers is contraindicated with regimens that include asunaprevir.

Source: Product monographs.[24-32]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of SOF/VEL for the treatment of chronic HCV infection in adults.

2.2 Methods

All manufacturer-provided trials considered pivotal in the manufacturer's submission were included in the systematic review. Other phase 3 studies were selected for inclusion based on the selection criteria presented in Table 7.

TABLE 7: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with chronic HCV infection Subpopulations: • Treatment history (treatment-naive, or prior relapse, partial response, null response, intolerant to, or ineligible to receive PR or DAA therapy) • Fibrosis level • Cirrhosis • HIV coinfection • Hepatitis B coinfection • Genotype subtype 1a or 1b • Renal insufficiency • Liver transplant • Decompensated liver disease • HCV RNA levels
Intervention	Sofosbuvir/velpatasvir 400 mg/100 mg once daily alone for 12 weeks for patients with chronic HCV infection who are without cirrhosis or with compensated cirrhosis Sofosbuvir/velpatasvir 400 mg/100 mg once daily in combination with ribavirin for 12 weeks for patients with chronic HCV infection who are with decompensated cirrhosis
Comparators	**Genotype 1** • Ledipasvir/sofosbuvir[a] • Ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavirin • Daclatasvir in combination with sofosbuvir ± ribavirin[a] • Asunaprevir in combination with daclatasvir for genotype 1b • Sofosbuvir in combination with ribavirin • Simeprevir in combination with sofosbuvir • Elbasvir/grazoprevir ± ribavirin • Placebo/no treatment. **Genotype 2** • Sofosbuvir in combination with ribavirin[a] • Daclatasvir in combination with sofosbuvir ± ribavirin[a] • Placebo in combination with PR • Placebo/no treatment. **Genotype 3** • Sofosbuvir in combination with ribavirin[a] • Daclatasvir in combination with sofosbuvir ± ribavirin[a] • Elbasvir/grazoprevir in combination with sofosbuvir (treatment-naive patients) • Sofosbuvir in combination with PR

	• Placebo in combination with PR • Placebo/no treatment **Genotype 4** • Ombitasvir/paritaprevir/ritonavir with ribavirin (non-cirrhotic patients) • Sofosbuvir in combination with PR • Asunaprevir in combination with daclatasvir and PR • Simeprevir in combination with PR • Elbasvir/grazoprevir ± ribavirin • Placebo in combination with PR • Placebo/no treatment. **Genotype 5** • Placebo in combination with PR • Placebo/no treatment **Genotype 6** • Placebo in combination with PR • Placebo/no treatment
Outcomes	**Key efficacy outcomes:** • Sustained virologic response[b] • Virologic failure • Relapse • Improvement in Child–Turcotte–Pugh[c] • Improvement in Model For End-Stage Liver Disease scores[c] • HRQoL[b] • Other patient-reported outcomes (e.g., symptom scales, measure of mental health, psychological/emotional distress)[b] • Mortality (all-cause and liver-related). **Other efficacy outcomes:** • Hepatic-related morbidity outcomes (e.g., histological changes, hepatocellular carcinoma, liver failure, liver transplant). **Harms outcomes:** • SAE, WDAE, AE Harms of special interest (nausea, fatigue, anemia, pruritus, headache, insomnia, ALT elevations, lipase elevations)
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; ALT = alanine aminotransferase; CHC = chronic hepatitis C; DAA = direct-acting antiviral agent; DB = double-blind; HCV = hepatitis C virus; HRQoL= health-related quality of life; PR = pegylated interferon plus ribavirin; RCT = randomized controlled trial; RNA = ribonucleic acid; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Used to treat patients with decompensated cirrhosis.
[b] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.
[c] In patients with decompensated cirrhosis.

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

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

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

The initial search was completed on May 24, 2016. Regular alerts were established to update the search until the CDEC meeting on September 21, 2016. 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). 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 8. There were no excluded studies as per APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 8 and described in section 3.2. As per APPENDIX 3: EXCLUDED STUDIES, there were not excluded studies.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

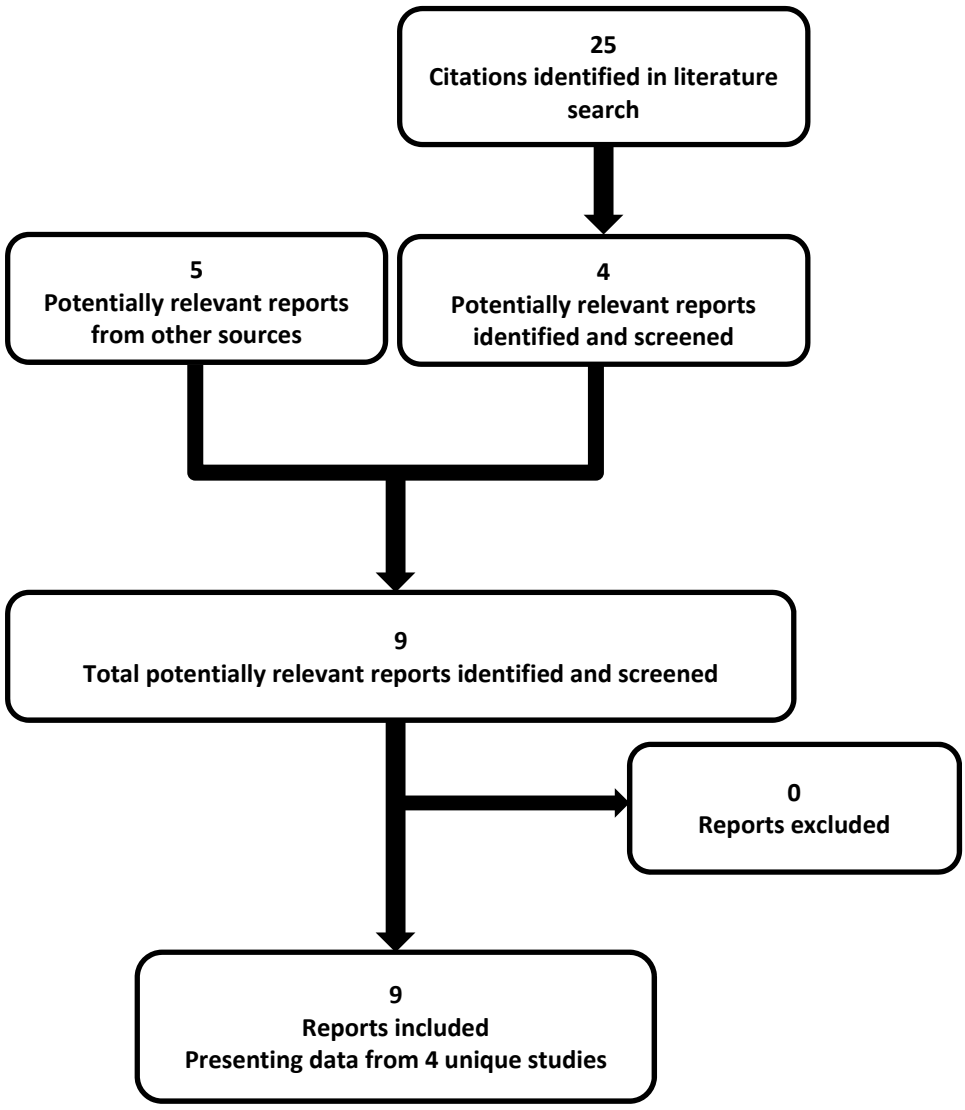

TABLE 8: DETAILS OF INCLUDED STUDIES

		ASTRAL-1	ASTRAL-2	ASTRAL-3	ASTRAL-4
DESIGNS & POPULATIONS	**Study Design**	DB, placebo-controlled, multi-centre RCT	Randomized, active-controlled, open-label, multi-centre trial	Randomized, active-controlled, open-label, multi-centre trial	Randomized, open-label, multi-centre trial
	Locations	81 centres in the United States, Canada, Europe, and Asia	51 centres in the United States	76 centres in the United States, Canada, in Australia, France, Germany, Italy, New Zealand, and the United Kingdom	47 centres in the United States
	Randomized (N)	741	269	558	268
	Inclusion Criteria	-Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at screening -At least a 6-month history of HCV infection -HCV treatment-naive or treatment-experienced (prior treatment failure to a regimen containing IFN either with or without RBV) with GTs 1, 2, 4, 5, 6, or indeterminate infection -Had documentation of the presence or absence of cirrhosis	-Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at screening -At least a 6-month history of HCV infection -HCV treatment-naive or treatment-experienced (prior treatment failure to a regimen containing IFN either with or without RBV) with GT2 -Had documentation of the presence or absence of cirrhosis	-Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at screening -At least a 6-month history of HCV infection -HCV treatment-naive or treatment-experienced (prior treatment failure to a regimen containing IFN either with or without RBV) with GT3 -had documentation of the presence or absence of cirrhosis	-Adults (aged ≥ 18 years) with HCV RNA levels ≥ 10,000 IU/mL at screening -At least a 6-month history of HCV infection -Chronic HCV infection of any genotype -Confirmed CTP class B (7–9) at screening -Confirmation of cirrhosis [redacted]
	Exclusion Criteria	-Prior exposure to SOF or other nucleotide analogue HCV NS5B inhibitor or any HCV NS5A inhibitor -Patients with a history of HCC -Solid organ transplant -Clinical hepatic decompensation (i.e., ascites, encephalopathy, or variceal hemorrhage) -Clinically significant illness (other than HCV) -Malignancy within 5 years of screening -Chronic liver disease of a non-HCV etiology -Coinfection with HIV or hepatitis B -Clinically relevant alcohol or drug abuse			-Prior exposure to SOF or other nucleotide analogue HCV NS5B inhibitor or any HCV NS5A inhibitor -Solid organ transplant -Inability to exclude HCC by imaging within 6 months of baseline -Clinically significant illness (other than HCV) -Malignancy within 5 years of screening -Chronic liver disease of a non-HCV

		ASTRAL-1	ASTRAL-2	ASTRAL-3	ASTRAL-4
		-CrCl < 60 mL/min -Platelets < 50,000/µL -Hemoglobin < 110 g/L for female patients and < 120 g/L for male patients			etiology -co-infection with HIV or hepatitis B -Clinically relevant alcohol or drug abuse [redacted] -CrCl < 50 mL/min -Platelets < 30,000/µL -Hemoglobin < 10 g/dL
DRUGS	**Intervention**	12 weeks of treatment with the fixed-dose combination of SOF with VEL (400 mg SOF/100 mg VEL)	12 weeks of treatment with the fixed-dose combination of SOF with VEL (400 mg SOF/100 mg VEL)	12 weeks of treatment with the fixed-dose combination of SOF with VEL (400 mg SOF/100 mg VEL)	-SOF/VEL (400 mg SOF/100 mg VEL) for 12 weeks[a] -SOF/VEL (400 mg SOF/100 mg VEL) + RBV for 12 weeks -SOF/VEL (400 mg SOF/100 mg VEL) for 24 weeks[a]
	Comparator(s)	-Placebo for 12 weeks (patients in the placebo group who completed treatment were eligible for treatment with SOF/VEL for 12 weeks in a deferred treatment study) - Benchmark rate of 85%	12 weeks of treatment with 400 mg SOF plus ribavirin	24 weeks of treatment with 400 mg SOF plus ribavirin	-None -Assumed spontaneous rate of 1%
DURATION	**Phase**				
	Double-blind	12 weeks	NA	NA	NA
	Open-label	NA	12 weeks	12 to 24 weeks	12 to 24 weeks
	Follow-up	24 weeks	24 weeks	24 weeks	24 weeks
OUTCOMES	**Primary End Point**	SVR12 versus benchmark rate	SVR12	SVR12	SVR12 versus spontaneous rate
		SVR12 for benchmark rate = 85%			SVR12 for spontaneous rate = 1%
	Other End Points	[redacted]			[redacted]

		ASTRAL-1	ASTRAL-2	ASTRAL-3	ASTRAL-4
		[redacted]			[redacted]
NOTES	**Publications**	Feld et al. 2015[35]	Foster et al. 2015[36]	Foster et al. 2015[36]	Curry et al. 2015[37]

CrCl = creatinine clearance; CHC = chronic hepatitis C; CLDQ-HCV = HCV-specific version of the Chronic Liver Disease Questionnaire; CTP = Child–Turcotte–Pugh; DB = double-blind; FACIT-Fatigue Scale = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; GT = genotype; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; Hgb = hemoglobin; HIV = Human Immunodeficiency Virus; IFN = interferon; MELD = Model for End-Stage Liver Disease; NA = not applicable; NS5A = nonstructural protein 5A; NS5B = nonstructural protein 5B; OL = open-label; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RCT = randomized controlled trial; RNA = Ribonucleic acid; SF-36 = Short Form (36) Health Survey; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; VEL = velpatasvir; WPAI = Work Productivity and Activity Impairment scores.

[a] Not a Health Canada–recommended dose; hence, not included in the review.

Note: 1 additional report was included.[38]

Source: Feld et al.;[35] Foster et al.;[36] Curry et al.;[37] Younossi et al.;[39] Clinical Study Reports: ASTRAL-1;[40] ASTRAL-2;[41] ASTRAL-3;[42] ASTRAL-4.[43]

3.2 Included studies

3.2.1 Description of Studies

A total of four pivotal phase 3 clinical trials were included in this review (ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4). The primary outcome in all trials was SVR12.

ASTRAL-1 (N = 741) was a phase 3, randomized, double-blind, placebo-controlled, multi-centre, international study that assessed the antiviral efficacy, safety, and tolerability of 12 weeks of the fixed-dose combination (FDC) regimen of SOF/VEL treatment compared with 12 weeks of placebo treatment among treatment-naive and previously treated patients with chronic genotype 1, 2, 4, 5, or 6 HCV infection, including those with compensated cirrhosis. Patients with chronic genotype 1, 2, 4, or 6 HCV infection were randomly assigned in a 5:1 ratio in a double-blind manner to receive SOF/VEL FDC (400 mg/100 mg) tablets once daily or matching placebo for 12 weeks. Patients with genotype 5 HCV infection were not randomized but were enrolled into the SOF/VEL for 12 weeks treatment group due to the low prevalence of genotype 5 in the study regions. Randomization was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) infection and the presence or absence of cirrhosis at screening. Patients in the placebo for 12 weeks treatment group with HCV RNA greater than the lower limit of quantitation (LLOQ) at the post-treatment week 12 visit (or post-treatment week 24 visit) were offered the option to participate in the deferred treatment study.

ASTRAL-2 (N = 269) was a phase 3, randomized, open-label, multi-centre study that assessed the antiviral efficacy, safety, and tolerability of 12 weeks of the FDC regimen of SOF/VEL treatment compared with 12 weeks of SOF + RBV treatment in treatment-naive and previously treated patients with chronic genotype 2 HCV infection, including those with compensated cirrhosis. Patients were randomly assigned in a 1:1 ratio to receive SOF/VEL FDC (400 mg/100 mg) tablets once daily for 12 weeks or SOF (400 mg) plus weight-based RBV for 12 weeks. Randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience (treatment-naive versus [vs.] treatment-experienced).

ASTRAL-3 (N = 558) was a phase 3, randomized, open-label, multi-centre study that assessed the antiviral efficacy, safety, and tolerability of 12 weeks of the FDC regimen of SOF/VEL treatment compared with 24 weeks of SOF + RBV treatment in treatment-naive and previously treated patients with chronic genotype 3 HCV infection, including those with compensated cirrhosis. Patients were randomly assigned in a 1:1 ratio to receive SOF/VEL FDC (400 mg/100 mg) tablets once daily for 12 weeks or SOF (400 mg) plus weight-based RBV for 24 weeks. Randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience (treatment-naive vs. treatment-experienced).

ASTRAL-4 (N = 268) was a phase 3, randomized, open-label, multi-centre study that assessed the antiviral efficacy, safety, and tolerability of the FDC regimen of SOF/VEL ± RBV for 12 weeks and the FDC regimen of SOF/VEL for 24 weeks in treatment-naive and previously treated patients with chronic genotypes 1 through 6 HCV infection who had decompensated cirrhosis (classified as Child–Turcotte–Pugh [CTP] class B). Patients were randomly assigned in a 1:1:1 ratio to receive SOF/VEL FDC (400 mg/100 mg) tablets once daily for 12 weeks, SOF/VEL FDC (400 mg/100 mg) tablets once daily plus weight-based RBV for 12 weeks, or SOF/VEL FDC (400 mg/100 mg) tablets once daily for 24 weeks. Randomization was stratified by HCV genotype (1, 2, 3, 4, 5, 6, and indeterminate). Patients who received SOF/VEL FDC (400 mg/100 mg) tablets once daily for 12 weeks and patients who received SOF/VEL FDC (400 mg/100 mg) tablets once daily for 24 weeks did not meet this review's inclusion

criteria. These treatment arms have not been summarized in this report because the regimen used was different from the Health Canada–approved regimen.

In ASTRAL-1, randomization was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) infection and the presence or absence of cirrhosis at screening; patients with genotype 5 HCV infection were not randomized but were enrolled into the SOF/VEL for 12 weeks treatment group due to the low prevalence of genotype 5 in the study regions. In ASTRAL-2 and ASTRAL-3 randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience (treatment-naive vs. treatment-experienced). In ASTRAL-4, randomization was stratified by HCV genotype (1, 2, 3, 4, 5, 6, and indeterminate). [redacted]

In ASTRAL-1, ASTRAL-2, and ASTRAL-3, approximately 20% of patients may have been treatment-experienced, and approximately 20% of patients may have had cirrhosis. In ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4, all patients were to complete the post-treatment week 4 and 12 visits regardless of their treatment duration. Patients who had HCV RNA < LLOQ at the post-treatment week 12 visit were also to complete the post-treatment week 24 visit unless a confirmed viral relapse occurred.

3.2.2 Populations

a) Inclusion and exclusion criteria

The main inclusion and exclusion criteria for the included trials are summarized in Table 8.

In the ASTRAL-1, ASTRAL-2, and ASTRAL-3 trials, eligible patients were males or non-pregnant/non-lactating females aged 18 years or older, with HCV RNA levels ≥ 10,000 IU/mL at the time of screening, and chronic HCV genotype 1, 2, 4, 5, 6, or indeterminate infection (ASTRAL-1), genotype 2 HCV infection (ASTRAL-2), genotype 3 HCV infection (ASTRAL-3), who were HCV treatment-naive (defined as having never been exposed to approved or experimental HCV-specific DAA agents or prior treatment of HCV with IFN or RBV) or treatment-experienced (defined as prior treatment failure to a regimen containing IFN either with or without RBV and with or without DAA agents that was completed at least eight weeks prior to baseline; patients must not have discontinued the prior regimen that resulted in virologic failure due to an AEs), and had documentation of the presence or absence of cirrhosis. In ASTRAL-4, eligible patients were males or non-pregnant/non-lactating females aged 18 years or older with chronic HCV infection of any genotype, with HCV RNA levels ≥ 10,000 IU/mL at the time of screening and decompensated cirrhosis, classified as CTP class B cirrhosis, who had not undergone liver transplantation.

The ASTRAL-1, ASTRAL-2, and ASTRAL-3 trials excluded patients with prior exposure to SOF or other nucleotide analogue HCV nonstructural protein (NS) 5B inhibitor or any HCV NS5A inhibitor, clinical hepatic decompensation (i.e., ascites, encephalopathy, or variceal hemorrhage), hepatitis B or HIV coinfection, malignancy, prior organ transplant, recent substance abuse, chronic liver disease of a non-HCV etiology, a history of HCC, clinically significant illness (other than HCV), chronic liver disease of a non-HCV etiology, creatinine clearance (CrCl) < 60 mL/min, platelets < 50,000/µL. ASTRAL-4 study excluded patients with prior exposure to SOF or other nucleotide analogue HCV NS5B inhibitor or any HCV NS5A inhibitor, hepatitis B or HIV coinfection, malignancy, prior organ transplant, recent substance abuse, chronic liver disease of a non-HCV etiology, clinically significant illness (other than HCV), chronic liver disease of a non-HCV etiology, CrCl < 50 mL/min, platelets < 30,000/µL. In addition, ASTRAL-4

excluded [redacted] or HCC cannot be excluded by imaging within six months of baseline.

b) Baseline characteristics

Across the studies, the mean age ranged from 49 to 58 years, and the proportion of males ranged from 55% to 76% (Table 9). In ASTRAL-1, ASTRAL-2, and ASTRAL-3, the proportion of patients with cirrhosis varied between trials (range 14% to 30%); however, the baseline characteristics between the randomized treatment groups were generally balanced. In ASTRAL-1, of the 624 patients in the SOF/VEL for 12 weeks treatment group, 328 patients (52.6%) had genotype 1 HCV infection, 104 patients (16.7%) had genotype 2 HCV infection, 116 patients (18.6%) had genotype 4 HCV infection, 35 patients (5.6%) had genotype 5 HCV infection, and 41 patients (6.6%) had genotype 6 HCV infection. In ASTRAL-4, of the 87 treated patients randomized to the SOF/VEL plus RBV for 12 weeks group, 68 (78%) had genotype 1 HCV infection (54 [62%] with genotype 1a and 14 [16%] with genotype 1b), four (5%) had genotype 2 HCV infection, 13 (15%) had genotype 3 HCV infection, two (2%) had genotype 4 HCV infection, and no patient had genotype 5 or 6 HCV infection. The majority of patients were treatment-experienced (47 of 87 patients: 54%) and had failed prior treatment with PR (27 of 47 patients: 57%) or DAA + PR (12 of 47 patients: 26%). The majority of patients had a baseline MELD score of ≤ 15 (83 of 87 patients: 95%). A minority of patients (10 of 87: 11.5%) who were CTP class B at screening were CTP class A or CTP class C at baseline, reflecting the dynamic changes in CTP parameters over time.

TABLE 9: SUMMARY OF BASELINE CHARACTERISTICS

	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 Weeks (n = 624)	**PBO 12 Weeks (n = 116)**	**SOF/VEL for 12 Weeks (n = 134)**	**SOF + RBV for 12 Weeks (n = 132)**	**SOF/VEL for 12 Weeks (n = 277)**	**SOF + RBV for 24 Weeks (n = 275)**	**SOF/VEL + RBV for 12 Weeks (n = 87)**
Age, mean (SD)	54 (10.9)	53 (10.4)	57 (10.6)	57 (9.3)	49 (10.4)	50 (10.0)	58 (6.9)
Male, n (%)	374 (60)	68 (59)	86 (64)	72 (55)	170 (61)	174 (63)	66 (76)
Race, n (%)							
White	493 (79)	90 (78)	124 (93)	111 (84)	250 (90)	239 (87)	79 (91)
Black or African-American	52 (8)	11 (9)	6 (4)	12 (9)	3 (1)	1 (< 1)	5 (6)
Asian	62 (10)	11 (9)	1 (1)	5 (4)	23 (8)	29 (11)	0
Other	14 (2)	4 (3)	[redacted]	[redacted]	1 (< 1)	[redacted]	3 (3)
HCV genotype, n (%)							
Genotype 1a	210 (34)	46 (40)	NA	NA	NA	NA	54 (62)
Genotype 1b	118 (19)	19 (16)	NA	NA	NA	NA	14 (16)
Genotype 2	104 (17)	21 (18)	134 (100)	132 (100)	NA	NA	4 (5)
Genotype 3	NA	NA	NA	NA	277 (100)	275 (100)	13 (15)
Genotype 4	116 (19)	22 (19)	NA	NA	NA	NA	2 (2)
Genotype 5	35 (6)	0	NA	NA	NA	NA	0
Genotype 6	41 (7)	8 (7)	NA	NA	NA	NA	0
Baseline HCV RNA							
log10 IU/mL, mean (SD)	6.3 (0.66)	6.3 (0.58)	6.5 (0.78)	6.4 (0.74)	6.2 (0.72)	6.3 (0.71)	5.8 (0.6)

	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 Weeks (n = 624)	**PBO 12 Weeks (n = 116)**	**SOF/VEL for 12 Weeks (n = 134)**	**SOF + RBV for 12 Weeks (n = 132)**	**SOF/VEL for 12 Weeks (n = 277)**	**SOF + RBV for 24 Weeks (n = 275)**	**SOF/VEL + RBV for 12 Weeks (n = 87)**
≥ 800 000 IU/mL	461 (74)	87 (75)	111 (83)	101 (77)	191 (69)	194 (71)	45 (52)
Compensated cirrhosis, n (%)	121 (19)	21 (18)	19 (14)	19 (14)	80 (29)	83 (30)	
Prior HCV Therapy, n (%)							
Treatment-naive	423 (68)	83 (72)	115 (86)	112 (85)	206 (74)	204 (74)	40/87 (46)
Treatment-experienced	201 (32)	33 (28)	19 (14)	20 (15)	71 (26)	71 (26)	47/87 (54)
Prior HCV Treatment, n/total n (%)							
DAA + peg-IFN + RBV	56/201 (28)	6/33 (18)	0	0	1/71 (1)	0	12/47 (26)
Peg-IFN + RBV	122/201 (61)	24/33 (73)	16/19 (84)	15/20 (75)	64/71 (90)	65/71 (92)	27/47 (57)
Other	23/201 (11)	3/33 (9)	3/19 (16)	5/20 (25)	6/71 (8)	6/71 (8)	8/47 (17)
Prior HCV Response, n/total n (%)							
Nonresponder	96/201 (48)	14/33 (42)	3/19 (16)	3/20 (15)	20/71 (28)	24/71 (34)	33/47 (70)
Relapse/Breakthrough	103/201 (51)	19/33 (58)	16/19 (84)	17/20 (85)	51/71 (72)	47/71 (66)	10/47 (21)
NA	2/201 (1)	0					4/47 (9)
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
Baseline CTP Score Category, n (%)							
CTP A [5 to 6]							6 (7)
CTP B [7 to 9]							77 (89)
CTP C [10 to12]							4 (5)
Baseline MELD Score Category, n (%)							
< 10							29 (33)
10 to 15							54 (62)
16 to 20							4 (5)
21 to 25							0
Baseline Ascites, n (%)							
None							22 (25)
Mild/Moderate							61 (70)
Severe							4 (5)

	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 Weeks (n = 624)	PBO 12 Weeks (n = 116)	SOF/VEL for 12 Weeks (n = 134)	SOF + RBV for 12 Weeks (n = 132)	SOF/VEL for 12 Weeks (n = 277)	SOF + RBV for 24 Weeks (n = 275)	SOF/VEL + RBV for 12 Weeks (n = 87)
Baseline Encephalopathy, n (%)							
None							33 (38)
Grade 1−2							54 (62)
Grade 3−4							0

CTP = Child–Turcotte–Pugh; DAA = direct-acting antiviral agent; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; MELD = Model for End-Stage Liver Disease; NA = not applicable; PBO = placebo; peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SD = standard deviation; SOF = sofosbuvir; VEL = velpatasvir.
Source: Feld et al.;[35] Foster et al.;[36] Curry et al.;[37] Clinical Study Reports: ASTRAL-1,[40] ASTRAL-2,[41] ASTRAL-3,[42] ASTRAL-4.[43]

3.2.3 Interventions

In the ASTRAL-1, ASTRAL-2, and ASTRAL-3 trials, SOF/VEL 400 mg/100 mg was administered as FDC tablets once daily for 12 weeks, while in ASTRAL-4, it was administered as FDC tablets once daily for either 12 weeks or 24 weeks. In the ASTRAL-4 study, patients in one of the treatment arms also received weight-based RBV (< 75 kg: 1,000 mg daily; ≥ 75 kg: 1,200 mg daily) in addition to SOF/VEL for 12 weeks. In the ASTRAL-1 study, patients were randomized to receive either SOF/VEL FDC tablets once daily or matching placebo for 12 weeks. ASTRAL-2 and ASTRAL-2 also included a control group that received SOF plus RBV for 12 weeks and 24 weeks, respectively. SOF was administered as 400 mg tablets once daily, and weight-based RBV (< 75 kg: 1,000 mg daily; ≥ 75 kg: 1,200 mg daily). Dose reduction or modification of SOF/VEL was not permitted. In ASTRAL-2, and ASTRAL-3, for patients who were receiving SOF plus RBV, a dose reduction of SOF was not permitted. In ASTRAL-2, ASTRAL-3, and ASTRAL-4, for patients who were receiving RBV, guidelines were in place for dose modifications and discontinuation of RBV based on the patient's hemoglobin concentration and cardiac status.

3.2.4 Outcomes

Outcome measures were consistent among the included trials. The primary efficacy outcome measure was the proportion of patients achieving SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs.

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

[redacted] which is an HRQoL instrument for patients with chronic liver disease. The HCV-specific version of the Chronic Liver Disease Questionnaire (CLDQ-HCV) measures Activity/Energy, Emotion, Worry, Systemic, and CLDQ-HCV Total score. Scores are based on a Likert scale from 0 (worst) to 7 (best) and measure Activity/Energy, Emotion, Worry, Systemic, and CLDQ-HCV Total score.[44] [redacted]

[redacted]

The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) contains 13 items and is scored using a 5-point Likert-type response scale to rate each item, where 0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much with a recall period of "during the past 7 days".[45] 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).[46] Although no information on the validity of FACIT-F or its minimal clinically important difference (MCID) in CHC 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.[47,48]

The Work Productivity and Activity Impairment questionnaire (WPAI) is an instrument used to measure the impact of a disease on work and daily activities. The work impairment domain is the sum of impairment in work productivity due to absenteeism (productivity loss due to a health-related absence from work, including personal time off, sick days off work, duration of short- or long-term disability, or worker's compensation days) and impairment due to decreased productivity while at work (reduced performance of productivity while at work due to health reasons, including time not spent on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work. Four main outcomes can be generated from the WPAI and expressed in percentages: 1) per cent work time missed due to health for those who were currently employed; 2) per cent impairment while working due to health for those who were currently employed and actually worked in the past seven days; 3) per cent overall work impairment due to health for those who were currently employed; 4) per cent activity impairment due to health 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 will 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.[49,50] Although no information on the validity of WPAI or its MCID in CHC patients was found, the MCID for the WPAI has been reported to be ≥ 7 percentage points in patients suffering from Crohn disease.[50]

The Short Form (36) Health Survey (SF-36) is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. SF-36 consists of eight domains: Physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Based on a panel of experts, the vitality dimension of SF-36 was considered most relevant for patients with CHC infection. In a systematic review that was conducted to identify and provide information on HRQoL instruments for CHC,[51] it was found that the largest impact of the disease was on role physical, role emotional, and general health. The individual domain scores can be aggregated to create a physical component summary (PCS) and a mental component summary (MCS). Scores for each component range from 0 to 100, with higher scores reflecting better HRQoL. The only information regarding the MCID in patients with CHC was for the SF-36 vitality dimension, for which the MCID was estimated by experts at 4.2 points (range 3 to 5). In general use of 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.[52] No MCID estimates in patients with CHC were found for the component scores or for domains other than vitality. It is unclear if the MCID estimates from other conditions or the general population are generalizable to HCV.

ASTRAL-4 employed the CTP and MELD scores to stage disease severity in patients with end-stage liver disease. The CTP and MELD are prognostic tools to classify patients with cirrhosis according to severity of disease. Both the CTP and MELD have been used to rank liver transplant candidates, with the MELD replacing the CTP in 2002 as a more objective measure that was able to assess the risk of mortality.

The CTP classification was originally developed in 1964 to evaluate the risk of surgical portosystemic shunt procedures, and was subsequently found to predict long-term survival in patients with cirrhosis.[53,54] A CTP score is calculated based on clinical and lab criteria, with points ranging from 1 to 3 assigned to specific criteria within five categories: Hepatic encephalopathy, ascites, total bilirubin, serum albumin, and international normalized ratio (INR). Points from each criterion are added to determine the CTP score and class: Class A, 5 to 6 points; class B, 7 to 9 points; class C, 10 to 15 points. The CTP classification can differentiate between patients with poor liver function and preserved liver function, and higher scores indicate worsening liver function.

The MELD score is calculated by combining four prognostic values (creatinine, bilirubin, INR, and the cause of cirrhosis) with their corresponding regression coefficients. Scores range from 6 to 40, with higher scores indicating more severe disease.[55] The MELD has been the method used for organ allocation for liver transplantation in the United States since 2002, where patients are ranked according to severity of liver disease and mortality risk.[56] Local and regional patients with sudden and severe onset liver failure (Status 1A) or very sick, chronically ill pediatric patients (Status 1B) get first allocation of livers.[57] For patients aged 12 years or older who fall outside these categories, livers are allocated according to the following ranking, with local candidates prioritized before regional and national candidates in the same score range:[57]

- Candidates with MELD score ≥ 35 (local, then regional)
- Candidates with MELD score ≥ 15 (local, then regional)
- Status 1a or 1b national candidates
- National candidates with MELD score ≥ 15
- Candidates with MELD score < 15 (local, regional, then national).

Further information regarding the validity of HRQoL instruments employed in the trials can be found in APPENDIX 5: VALIDITY OF OUTCOME MEASURES.

a) Harms

An adverse event (AE) was defined as any untoward medical occurrence in a clinical study patient administered a study drug, which did not necessarily have a causal relationship with the treatment. An AE could therefore have been any unfavourable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. AEs also included pre-treatment or post-treatment complications that occurred as a result of protocol-specified procedures, lack of efficacy, overdose, drug abuse or misuse reports, or occupational exposure. Pre-existing events that increased in severity or changed in nature during or as a consequence of participation in the clinical study were also considered AEs.

3.2.5 Statistical analysis

In ASTRAL-1, it was estimated that [redacted] in SVR12 rate from the performance goal of 85% by using a two-sided exact one-sample binomial test at the 0.05 significance level. The two-sided one-sample binomial test was used to test the statistical

hypotheses. The two-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method was provided for the SVR12 rate for the SOF/VEL 12-week treatment group. The performance goal of 85% was chosen because [redacted] Hence, a high benchmark of 85% was set. The point estimates and the two-sided 95% exact CIs of the SVR12 rates for the SOF/VEL 12-week treatment group was estimated by [redacted]

In ASTRAL-2, it was estimated that [redacted] to establish noninferiority of the SVR12 rates between the two groups. This power calculation was based on the assumptions that the noninferiority margin would be 10%, [redacted] A closed testing procedure was used whereby the noninferiority of SOF/VEL for 12 weeks to SOF + RBV for 12 weeks was first assessed by comparing the lower bound of the two-sided 95% CI (using stratum-adjusted Mantel–Haenszel [MH] proportions) to −10%. If the lower bound of the CI was greater than −10% (i.e., the null hypothesis for noninferiority was rejected), then a two-sided stratified Cochran–Mantel–Haenszel (CMH) test was used to test for the superiority of SOF/VEL for 12 weeks over SOF + RBV for 12 weeks at a significance level of 0.05. If the null hypotheses for noninferiority and superiority were both rejected, then superiority of SOF/VEL over SOF + RBV was established. If the null hypothesis for noninferiority was rejected and there was insufficient evidence to reject the null hypothesis for superiority, then only noninferiority was demonstrated. If there was insufficient evidence to reject the null hypothesis for noninferiority, then neither noninferiority nor superiority was demonstrated. The statistical justification of a noninferiority margin was based on a two-step process in which the treatment benefit of SOF + RBV for 12 weeks over SOF alone given for 12 weeks was first estimated, then a margin that preserved some fraction of the treatment benefit characterized in the first step was defined. The SVR12 rates of SOF + RBV 12-week regimen as well as the SOF-alone 12-week regimen for genotype 2 patients were estimated through a comprehensive Bayesian constrained modelling approach. [redacted]

In ASTRAL-3, it was estimated that 250 patients need to be randomized to each treatment group in order to provide 94% power to establish noninferiority of the SVR12 rates between the two groups. This power calculation was based on the assumptions that the noninferiority margin would be 10%, both groups would have an SVR12 rate of 89%, and the one-sided significance level was 0.025. A closed testing procedure was used, whereby the noninferiority of SOF/VEL for 12 weeks to SOF + RBV for 24 weeks was first assessed by comparing the lower bound of the two-sided 95% CI (using stratum-adjusted MH proportions) to −10%. If the lower bound of the CI was greater than −10% (i.e., the null hypothesis for noninferiority was rejected), then a two-sided stratified CMH test was used to test for the superiority of SOF/VEL for 12 weeks over SOF + RBV for 12 weeks at a significance level of 0.05. If the null hypotheses for noninferiority and superiority were both rejected, then superiority of SOF/VEL over SOF + RBV was established. If the null hypothesis for noninferiority was rejected and there was insufficient evidence to reject the null hypothesis for superiority, then only noninferiority was demonstrated. If there was insufficient evidence to reject the null hypothesis for noninferiority, then neither noninferiority nor superiority was demonstrated. The statistical justification of a noninferiority margin was based on a two-step process in which the treatment benefit of SOF + RBV for 24 weeks over SOF alone given for 12 weeks was first estimated, then a margin that preserved some fraction of the treatment benefit characterized in the first step was defined. Based on the phase 3 VALENCE trial,[23] the SVR12 rate for SOF + RBV 24 weeks was 85.2% (213/250) [redacted] Based on pooled meta-analysis results from these studies, the SVR12 for SOF alone given for 12 weeks was estimated to be 54.3% [redacted] Based on these estimates, a noninferiority margin of 10% would [redacted]

In ASTRAL-4, it was estimated that 75 patients needed to be randomized in each treatment group to provide > 99% power to detect at least a 40% improvement in SVR12 rate from the assumed spontaneous rate of 1% or less. In the primary efficacy analysis, the SVR12 rate in each of the three treatment groups was compared with the assumed spontaneous rate of 1%. To control the overall type I error, each comparison was tested at the significance level of 0.0167 using a Bonferroni adjustment. This 1% spontaneous rate was assumed in the statistical test of treatment benefit because at the time of the trial, there were no available treatment options for these patients and non-treatment rarely results in spontaneous cure. [redacted]

In all four trials, for the analyses of categorical HCV RNA data, if a data point is missing and is preceded and followed in time by values that are deemed successes, then the missing data point was considered a success; otherwise, the data point was considered a failure. [redacted]. If no HCV RNA values were obtained after the last dose of study medication, the patient was considered a treatment failure for the SVR end points. A patient who achieved SVR12 and had no further HCV RNA measurements collected was counted as having achieved SVR24 due to the high correlation between these two end points.

[redacted] (percentage of overall work impairment due to HCV infection for patients who worked in the past week and percentage of activity impairment due to HCV infection for all patients) [redacted] Although inferential statistics (*P* values) were presented, the results should be interpreted with caution, as multiple end points were being tested, and the study was not powered to test these exploratory end points. [redacted]

Analysis populations

[redacted]

The full analysis set (FAS) included patients who were randomized into the study and received at least one dose of study drug. Patients were grouped within the FAS by the treatment group to which they were randomized. The FAS was the primary analysis set for efficacy analyses.

The safety analysis set included all patients who were randomized into the study and received at least one dose of study drug. [redacted] The safety analysis set was the primary analysis set for safety analyses.

3.3 Patient disposition

Between [redacted] of patients screened in the trials did not enter the treatment phase; the most common reason stated was [redacted] (Table 10). Discontinuation rates were low in most of the trials, with the proportion of patients who discontinued study medication ranging from 0.3% to 7.6%. The highest discontinuation rate was in the ASTRAL-3 trial in the SOF + RBV for 24 weeks treatment arm.

TABLE 10: PATIENT DISPOSITION

	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 Weeks	**PBO 12 Weeks**	**SOF/VEL for 12 Weeks**	**SOF + RBV for 12 Weeks**	**SOF/VEL for 12 Weeks**	**SOF + RBV for 24 Weeks**	**SOF/VEL + RBV for 12 Weeks**
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]
Randomized, N	741		269		558		268
Enrolled, N	625	116	135	134	278	280	88
Enrolled and treated, n (%)	624 (99.8)	116 (100)	134 (99.3)	132 (98.5)	277 (99.6)	275 (98.2)	87 (98.9)
Completed treatment, n (%)	622 (99.7)	113 (97.4)	133 (99.3)	131 (99.2)	275 (99.3)	254 (92.4)	82 (94.3)
Discontinued treatment, n (%)	2 (0.3)	3 (2.6)	1 (0.7)	1 (0.8)	2 (0.7)	21 (7.6)	5 (5.7)
Adverse event	1 (0.2)	2 (1.7)	1 (0.7)	0	0	9 (3.3)	4 (4.6)
Lost to follow-up	1 (0.2)	0	0	1 (0.8)	0	4 (1.5)	0
Investigator's discretion	0	1 (0.9)	0	0	0	0	0
Noncompliance with study drug	0	0	0	0	1 (0.4)	2 (0.7)	0
Withdrew consent	0	0	0	0	0	3 (1.1)	0
Death	0	0	0	0	0	2 (0.7)	0
Lack of efficacy	0	0	0	0	1 (0.4)	1 (0.4)	1 (1.1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full analysis set, N	624 (99.8)	116 (100)	134 (99.3)	132 (98.5)	277 (99.6)	275 (98.2)	87 (98.9)
Safety, N	624 (99.8)	116 (100)	134 (99.3)	132 (98.5)	277 (99.6)	275 (98.2)	87 (98.9)

PBO = placebo; SOF = sofosbuvir; VEL = velpatasvir.
Source: Feld et al.;[35] Foster et al.;[36] Curry et al.;[37] Clinical Study Reports: ASTRAL-1, [40] ASTRAL-2,[41] ASTRAL-3,[42] ASTRAL-4.[43]

3.4 Exposure to study treatments

Treatment durations were consistent with assigned treatment arm assignments in each of the trials. In ASTRAL-1, the mean durations of treatment were [redacted], and [redacted] in the SOF/VEL for 12 were [redacted], and [redacted] in the SOF/VEL for 12 weeks and SOF plus RBV for 12 weeks treatment arms, respectively. In ASTRAL-3, the mean durations of treatment were [redacted], and [redacted] in the SOF/VEL for 12 weeks and SOF plus RBV for 24 weeks treatment arms, respectively. In ASTRAL-4, the mean durations of treatment was [redacted] in the SOF/VEL + RBV for 12 weeks treatment arm (Table 11).

TABLE 11: EXPOSURE TO STUDY INTERVENTION

	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 Weeks (n = 624)	PBO 12 Weeks (n = 116)	SOF/VEL for 12 Weeks (n = 134)	SOF + RBV for 12 Weeks (n = 132)	SOF/VEL for 12 Weeks (n = 277)	SOF + RBV for 24 Weeks (n = 275)	SOF/VEL + RBV for 12 Weeks (n = 87)
[redacted]							
[redacted]							
[redacted]							
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PBO = placebo; SOF = sofosbuvir; VEL = velpatasvir.
Source: Clinical Study Reports: ASTRAL-1,[40] ASTRAL-2,[41] ASTRAL-3,[42] ASTRAL-4.[43]

3.5 Critical appraisal

3.5.1 Internal validity

Randomization and allocation concealment in ASTRAL-1 were well reported and shown to be effective based on similar distribution of baseline characteristics between different treatment arms. All included

trials except ASTRAL-1 were open label; while SVR12 is an objective measure and may not be largely affected by an open-label design, being aware of treatment allocation might have influenced subjective measures, such as HRQoL measures and reporting of AEs, and influenced a patient's decision to continue or discontinue treatment and/or adherence. In the ASTRAL-1 trial, all patients with genotype 5 were enrolled in the SOF/VEL 12 weeks treatment arm; hence, these patients might have been aware of treatment allocation, and might have influenced subjective measures, such as HRQoL measures and reporting of AEs. This uneven distribution of genotype 5 also limits the generalizability of the results for this particular population.

In all trials, imputation and handling methods used for the missing data for the SVR seem appropriate.

ASTRAL-1 compared the SVR12 resulting from treatment with a performance goal of 85%; however, it is unclear how it was chosen. ASTRAL-4 compared SVR12 rate versus a spontaneous rate of 1%; however, there are currently other treatments indicated for patients with HCV who have decompensated cirrhosis against which ASTRAL-4 could have made comparisons. Despite the limitations associated with the design of the ASTRAL-1 and ASTRAL-4 trials, this trial design for new drug regimens is accepted by the FDA in the treatment of CHC infection.[58] However, the draft guidance document produced by the FDA noted that future treatments should use alternate study designs with an active control once pegylated interferon–free regimens are available.

ASTRAL-2 and ASTRAL-3 were adequately powered for the noninferiority analyses. Only the intention-to-treat (ITT) analysis was used in this calculation, which tends to bias toward achieving noninferiority versus a per-protocol (PP) analysis. However, as most patients completed the trial, the two populations would not be expected to differ greatly.

Patient-reported outcomes (PROs) were exploratory efficacy end points and there were no multiplicity adjustments applied to the PRO variables; hence, results of the PROs ([redacted]) should be interpreted with caution, where a statistically significant finding for the comparison for these outcomes is more likely subject to inflated type I error rate (alpha). In addition, there was a lack of data imputation for missing PROs data; such missing data are unlikely to be missing at random (usually sicker patients are missing), which could lead to overestimates in HRQoL and/or other PROs. A considerable proportion of patients ([redacted]) were missing from the baseline analyses of PROs, and more than that were missing at later points in the study. The *P* values for the between-treatment group comparisons were based on a [redacted], which is a non-parametric statistical test and assesses whether mean ranks differ, and differences in between-treatment groups with the corresponding 95% CI for the treatment difference were not estimated. Therefore, it is not possible to judge whether the difference between treatment groups is clinically meaningful. Finally, MCIDs specific to CHC PROs are unknown, which limits the ability to interpret these results.

The 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.

External Validity

Overall, the four trials represent a population with chronic HCV infection and minimal comorbidities. Generalizability of trial results may be limited for more complex patients, as important and common comorbidities, including HIV coinfection, were listed as exclusion criteria for all four trials. A relatively

large percentage of patients are coinfected with HCV and HIV, and there is evidence that HIV coinfection can accelerate progression of CHC to important complications such as cirrhosis and end-stage liver disease. In April 2016, data were presented at a conference for a recently completed single-arm, open-label trial of 106 patients with CHC and HIV coinfection, which suggests that SVR12 rates of 95% were achieved in a pool of patients with genotype 1, 2, 3, and 4 and coinfected with HIV.[59] However, these data have not been published and full results are not yet available.

Only a relatively small number of patients (up to 30%) in ASTRAL-1, ASTRAL-2, and ASTRAL-3 had cirrhosis, limiting the extent of evidence in this population.

A considerable proportion of patients ([redacted]) were screened in the trials but did not enter the treatment phase. The most common reason stated was [redacted]. All trials excluded patients with hepatitis B coinfection, malignancy, and recent substance 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. However, the ASTRAL-4 trial included patients who have decompensated liver disease; the inclusion of such patients in this trial helps improve the generalizability of the results.
Because the ASTRAL-1 and ASTRAL-4 trials were not actively controlled, the efficacy of SOF/VEL therapy compared with existing treatments cannot be established directly from these studies. The manufacturer did not submit an indirect treatment comparison in order to compare with other regimens; thus, it is difficult to determine the comparative effectiveness and place in therapy, relative to other regimens currently in use in Canada.

In ASTRAL-4, there were limited data available in patients with genotypes 2 or 4 HCV, and no patients with genotypes 5 or 6 HCV were enrolled in the SOF/VEL + RBV treatment arm. Hence, there is uncertainty about whether the SVR rates from the overall population (mainly patients with genotype 1) would be seen in clinical practice.

A considerable proportion of data ([redacted]) for the PRO SF-36, CLDQ-HCV, FACIT-F, and WPAI-Hep C was missing. This may compromise the generalizability of the results of these outcomes.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (section 2.2, Table 7). See 0 for detailed efficacy data.

3.6.1 Sustained virologic response

In the ASTRAL-1 study, which included patients with genotypes 1, 2, 4, 5, or 6 HCV infection, the SOF/VEL for 12 weeks treatment group met the primary end point of an SVR12 rate that was statistically superior relative to the pre-specified performance goal of 85% ($P < 0.001$). In the SOF/VEL for 12 weeks treatment group, 99.0% (95% CI, 97.9% to 99.6%) of patients (618 of 624) achieved SVR12 (Table 13). High SVR12 rates were achieved in all subgroups across all HCV genotypes (genotype 1, 2, 4, 5, or 6 HCV infection). Among patients in the SOF/VEL for 12 weeks treatment group, the SVR12 rate in patients with cirrhosis was 99.2%, and in patients without cirrhosis, it was 99.0%. The SVR12 rate in the SOF/VEL for 12 weeks treatment group in patients with prior treatment failure was 99.5% and in treatment-naive patients was 98.8%. All patients previously treated with a DAA + PR achieved SVR12 (56 of 56: 100%), which included 48, six, and two patients with genotype 1, 4, and 5 HCV infection, respectively (Table 13). No patient in the placebo for 12 weeks treatment group (0 of 116) achieved SVR12.

In the ASTRAL-2 study, which included patients with genotype 2 HCV infection, the SOF/VEL for 12 weeks treatment group met the primary end point of an SVR12 rate that was noninferior to the SVR12 rate in the SOF + RBV for 12 weeks treatment group. In the SOF/VEL for 12 weeks treatment group, 99.3% (95% CI, 95.9% to 100%) of patients (133 of 134) achieved SVR12, while in the SOF + RBV for 12 weeks treatment group, 93.9% (95% CI, 88.4% to 97.3%) of patients (124 of 132) achieved SVR12. The strata-adjusted difference (95% CI) in the proportions was 5.2% (0.2% to 10.3%) (Table 14). Because the lower bound of the two-sided 95% CI for the difference between groups was greater than the pre-specified noninferiority margin of −10%, the efficacy of SOF/VEL for 12 weeks was demonstrated to be statistically noninferior to SOF + RBV for 12 weeks. There was also sufficient evidence to demonstrate the statistical superiority of treatment with SOF/VEL for 12 weeks over SOF + RBV for 12 weeks for SVR12 (P = 0.018; CMH test stratified by cirrhosis status and prior treatment experience). The high SVR12 rates observed in both treatment groups, with no cases of virologic failure in the SOF/VEL for 12 weeks treatment group and six cases of virologic failure in the SOF + RBV for 12 weeks treatment group, precluded meaningful interpretation of subgroup analyses. [redacted] (Table 14). No formal statistical comparison was undertaken for these subgroups between the SOF/VEL for 12 weeks and SOF + RBV for 12 weeks treatment groups.

In the ASTRAL-3 study, which included patients with genotype 3 HCV infection, the SVR12 rate for the SOF/VEL for 12 weeks treatment group was statistically noninferior to the SVR12 rate for the SOF + RBV for 24 weeks treatment group. In the SOF/VEL for 12 weeks treatment group, 95.3% (95% CI, 92.1% to 97.5%) of patients (264 of 277) achieved SVR12, while in the SOF + RBV for 24 weeks treatment group, 80.4% (95% CI, 75.2% to 84.9%) of patients (221 of 275) achieved SVR12. The strata-adjusted difference in the proportions was 14.8% (95% CI, 9.6% to 20.0%). Because the lower bound of the two-sided 95% CI for the difference between groups was greater than the pre-specified noninferiority margin of −10%, the efficacy of SOF/VEL for 12 weeks was demonstrated to be statistically noninferior to SOF + RBV for 24 weeks. The superiority of treatment with SOF/VEL for 12 weeks over SOF + RBV for 24 weeks for SVR12 was also demonstrated (P < 0.001; CMH test stratified by cirrhosis status and prior treatment experience). Within each treatment group, the SVR12 rates for most subgroups were generally consistent with those observed in the overall population. In the SOF/VEL for 12 weeks treatment group, the SVR12 rates for patients with and without cirrhosis were 91.3% (73 of 80) and 97.0% (191 of 197), respectively, and the SVR12 rates for treatment-naive and treatment-experienced patients were 97.1% (200 of 206) and 90.1% (64 of 71), respectively. Among patients in the SOF/VEL for 12 weeks treatment group, the SVR12 rates were ≥ 90% across all pre-specified subgroups, with the exception of SVR12 rates of 89.1% (57 of 64) in patients who received a prior PR regimen, and 85.0% (17 of 20) in patients who were non-responders to prior HCV treatment. The SVR12 in the SOF/VEL for 12 weeks treatment group was achieved by 89.2% (33 of 37) of patients who were treatment-experienced and cirrhotic, while it was achieved by 91.2% (31/34) of patients who were treatment-experienced and non-cirrhotic. In the SOF + RBV for 24 weeks treatment group, patients with cirrhosis had considerably lower SVR12 rates (55 of 83: 66.3%) than patients without cirrhosis (163 of 187: 87.2%), and patients with prior treatment experience had considerably lower SVR12 rates (45 of 71: 63.4%) than treatment-naive patients (176 of 204: 86.3%) (Table 14). No formal statistical comparison was undertaken for these subgroups between SOF/VEL for 12 weeks and SOF + RBV for 24 weeks treatment groups.

In the ASTRAL-4 study, which included patients with genotype chronic genotypes 1, 2, 3, or 4 HCV infection who had decompensated cirrhosis, the SVR12 rate for the SOF/VEL + RBV for 12 weeks

treatment group was 94.3% (95% CI, 87.1% to 98.1%) of patients (82 of 87). The SOF/VEL + RBV for 12 weeks treatment group met the primary efficacy end points with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%. The *P* value was < 0.001 for the comparison with the SVR12. Among patients with genotype 1 HCV infection, the SVR12 rate was 95.6% (65 of 68); among patients with genotype 3 HCV infection, the SVR12 rate was 84.6% (11 of 13). All patients with genotype 2 or 4 HCV infection achieved SVR12 (Table 15). Treatment with SOF/VEL + RBV for 12 weeks resulted in high SVR12 rates irrespective of genotype, prior treatment history, baseline HCV RNA, and presence of pre-treatment NS5A or NS5B resistance-associated variants (RAVs) (Table 15 and Table 20).

3.6.2 Response by resistance-associated variants

In the ASTRAL-1 study, approximately [redacted] and [redacted] of patients in the SOF/VEL for 12 weeks treatment group had baseline NS5A RAVs and NS5B RAVs, respectively. Baseline NS5A or NS5B RAVs had no impact on SVR12, with high SVR12 across all subtypes and/or genotypes regardless of the presence of NS5A RAVs or NS5B RAVs. Two patients had virologic failure and both had baseline NS5A RAVs. At virologic failure time points, both patients developed additional NS5A RAVs (Y93N and Y93H) that conferred a high (> [redacted]) fold shift in EC50 to VEL. No NS5B RAVs were detected at baseline or post-treatment in either patient with virologic failure (Table 16).

In the ASTRAL-2 study, approximately [redacted] and [redacted] of patients in the SOF/VEL for 12 weeks treatment group had pre-treatment NS5A and NS5B RAVs, respectively. The most prevalent NS5A RAV observed was [redacted]. Despite the presence of pre-treatment NS5A and NS5B RAVs, no patient in the SOF/VEL for 12 weeks treatment group experienced virologic failure in this study (Table 17). Two of the six patients who relapsed in the SOF + RBV for 12 weeks treatment group had low levels of the NS5B NI RAV L159F detectable at failure.

In the ASTRAL-3 study, pre-treatment NS5A and NS5B nucleoside inhibitor (NI) RAVs were present in [redacted] and [redacted] of patients, respectively, in the SOF/VEL for 12 weeks treatment group. There was a numerically lower SVR12 rate in SOF/VEL-treated patients with baseline NS5A RAVs compared with patients without NS5A RAVs (88% versus [vs.] 97%, respectively) (Table 18). All patients with NS5B NI RAVs in the SOF/VEL for 12 weeks treatment group achieved SVR12. A total of 10 patients in the SOF/VEL for 12 weeks treatment group relapsed, and one patient was reinfected. All 10 patients had the NS5A RAV Y93H detected at relapse time points (Table 19). No SOF/VEL-treated patients had NS5B NI RAVs emerge at relapse. The NS5B NI RAVs (N142T, L159F, or V321A) emerged in seven of 39 patients in the SOF + RBV for 24 weeks treatment group who had virologic failure.

In the ASTRAL-4 study, in the SOF/VEL + RBV for 12 weeks treatment group, pre-treatment NS5A RAVs were observed in [redacted] of patients. The presence of pre-treatment NS5A RAVs did not affect treatment outcome. In genotype 1 HCV-infected patients, the SVR12 rates in patients with or without pre-treatment RAVs were similar in the SOF/VEL + RBV for 12 weeks treatment group. All patients with genotype 2 or 4 HCV infection achieved SVR12 irrespective of the presence of pre-treatment RAVs. Interpretation of the analyses of the impact of NS5A RAVs on treatment outcome in patients with genotype 3 HCV infection is limited by the small number of patients with NS5A RAVs.

In patients with genotype 3 HCV infection who did not have pre-treatment RAVs, the SVR12 rate was [redacted]. In the SOF/VEL + RBV for 12 weeks treatment group, three patients (one with genotype 1a and two with genotype 3a) experienced virologic failure. One patient with genotype 1a HCV

infection had no NS5A or NS5B RAVs at failure. One patient with genotype 3a HCV infection had Y93H emerge at failure. Another patient with genotype 3a HCV infection had HCV with Y93H at pre-treatment and relapse, and also developed low levels of NS5B N142T+E237G at failure. This patient had undetectable drug levels, consistent with study drug non-adherence. The presence of pre-treatment NS5B RAVs did not impact treatment outcome in any treatment group.

3.6.3 Relapse and on-treatment failure

In the ASTRAL-1 study, a total of six of 624 patients (1.0%) who received SOF/VEL did not achieve SVR12. Two patients had relapse determined at post-treatment week 4; one treatment-naive patient with genotype 1a HCV infection without cirrhosis and one treatment-experienced patient with genotype 1b infection and cirrhosis. Four additional patients (three with genotype 1 and one with genotype 5) did not achieve SVR12 (one patient withdrew consent, two patients did not return for the post-treatment week 12 visit, and one patient died prior to their post-treatment week 4 visit).

In the ASTRAL-2 study, in the SOF/VEL for 12 weeks treatment group, one of 134 patients (0.7%) did not achieve SVR12: The patient discontinued study treatment on day 1 (after receiving one dose) due to AEs of [redacted]. In the SOF + RBV for 12 weeks treatment group, eight of 132 patients (6.1%) did not achieve SVR12. Of these, six patients relapsed and two were lost to follow-up. Four relapses occurred by the post-treatment week 4 visit and two relapses occurred between the post-treatment week 4 and 12 visits.

In the ASTRAL-3 study, in the SOF/VEL for 12 weeks treatment group, 13 of 277 patients (4.7%) did not achieve SVR12. Of these, no patient had on-treatment virologic failure, 11 patients relapsed, and two patients were lost to follow-up. In the SOF + RBV for 24 weeks treatment group, 54 of 275 patients (19.6%) did not achieve SVR12. Of these, one patient had on-treatment virologic failure (non-response), 38 patients relapsed, and 15 patients did not achieve SVR12 for reasons other than virologic failure. These 15 patients included [redacted]

In the ASTRAL-4 study, the virologic failure rate in the SOF/VEL + RBV for 12 weeks treatment group was 3.4%, with 2.4% of patients (2 of 85) relapsed and 1.1% (1 of 87) had on-treatment virologic failure. One patient (1.5%) with genotype 1 HCV infection and two patients (15.4%) with genotype 3 HCV infection had virologic failures. There were no virologic failures in patients with genotype 2 or 4 HCV infection.

3.6.4 Improvement in model for end-stage liver disease scores

ASTRAL-4 assessed improvement in MELD scores. Overall, the majority of patients who received SOF/VEL + RBV for 12 weeks and achieved SVR12 also had a decrease (improvement) (41 of 81 patients: 50.6%) in MELD score between baseline and post-treatment week 12 (range [redacted]) (Table 21). Among patients who had MELD score < 15 at baseline and achieved SVR12, 68 of 71 patients (95.8%) remained < 15 at post-treatment week 12. A total of four patients (40.0%) with baseline MELD score ≥ 15 who achieved SVR12 improved to < 15 (Table 22).

Among the 71 patients who had MELD score < 15 at baseline and achieved SVR12, and for whom MELD data were available at post-treatment week 12, a total of [redacted] had an improved MELD score (15 patients [21.1%] had a decrease of 1 point in MELD score, 10 patients [14.1%] had a decrease of 2 points, four patients [5.6%] had a decrease of 3 points, one patient [1.4%] had a decrease of 4 points, two patients [2.8%] had a decrease of 5 points, and two patients [2.8%] had a decrease of 6 points; none of the patients had a decrease of more than 6 points in MELD score), 10 (14.1%) had no change in the MELD score, and 27 (38%) had a worsening in the MELD score (12 patients [16.9%] had an increase of 1 point in MELD score, 11 patients [15.5%] had an increase of 2 points, three patients [4.2%] had an increase of 4 points, and one patient [1.4] had an increase of 11 points in MELD score; no patient had an increase of more than 11 points) (Table 21). Of the 10 patients who had a baseline MELD score of 15 or more, seven (70%) had an improved MELD score (three patients [30%] had a decrease of 1 point in MELD score, two patients [20%] had a decrease of 3 points, one patient [10%] had a decrease of 4 points, and one patient [10%] had a decrease of 8 points, none of the patients had a decrease of more than 8 points in MELD score), two (20%) had no change in the MELD score, and one (10%) had a worsening in the MELD score (one patient [10.0%] had an increase of 3 points) (Table 21).

Improvements in MELD score were largely due to improvements in total bilirubin; changes in creatinine and INR were minimal (Table 23).

[redacted] (Table 24).

3.6.5 Improvement in Child–Turcotte–Pugh

ASTRAL-4 assessed improvement in CTP scores. Among patients who received SOF/VEL + RBV for 12 weeks and achieved SVR12, 33 patients (40.7%) had an improvement in CTP score (range: [redacted]) while 40 patients (49.4%) had no change. [redacted] (Table 25).

[redacted]
(Table 27).

Overall, among patients who had CTP class B cirrhosis at baseline and achieved SVR12, 63 of 72 patients (87.5%) remained CTP class B at post-treatment week 12. A total of eight patients (11.1%) with baseline CTP class B cirrhosis who achieved SVR12 improved to CTP class A and one patient (1.4%) worsened to CTP class C at post-treatment week 12. [redacted] Of the four patients who had CTP class C cirrhosis at baseline and achieved SVR12, no patient improved to CTP class A, 1 patient (25%) improved to CTP class B, and three patients (75%) remained at CTP class C (Table 26).

3.6.6 Health-Related Quality of Life

[redacted]

[redacted]

3.6.7 Other patient-reported outcomes

[redacted]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Table 33 for detailed harms data.

3.7.1 Adverse events

The proportion of patients who reported AEs ranged from [redacted] to [redacted] while on SOF/VEL for 12 weeks, 90.8% among those who received SOF/VEL + RBV for 12 weeks; among those who received SOF + RBV for 12 weeks and SOF + RBV for 24 weeks, the frequency was 76.5% and 94.5%, respectively, and among those who received placebo, the frequency of AEs was 76.7% (Table 12).

In the ASTRAL 1 trial, the three most common reported AEs were headache ([redacted]), fatigue ([redacted]), and nasopharyngitis ([redacted]) in patients who received SOF/VEL for 12 weeks, while for those who received placebo for 12 weeks, it was headache (33 patients: 28.4%), fatigue (23 patients: 19.8%), and nausea (13 patients: 11.2%). In ASTRAL-2, the three most common reported AEs were headache ([redacted]), fatigue ([redacted]), and nausea ([redacted]) in patients who received SOF/VEL for 12 weeks, while in those who received SOF +

RBV for 12 weeks, they were fatigue (47 patients: 35.6%), headache (29 patients: 22.0%), and nausea (19 patients: 14.4%). In ASTRAL-3l, the three most common reported AEs were headache ([redacted]), fatigue ([redacted]), and nausea ([redacted]) in patients who received SOF/VEL for 12 weeks, while in those who received SOF + RBV for 24 weeks, they were fatigue (105 patients: 38.2%), headache (89 patients: 32.4%), and insomnia (74 patients: 26.9%). In ASTRAL-4, the three most common reported AEs among patients who received SOF/VEL + RBV for 12 weeks were fatigue (34 patients: 39.1%), anemia (27 patients: 31.0%), and nausea (22 patients: 25.3%) (Table 33).

3.7.2 Serious adverse events

The rates of serious adverse events (SAEs) ranged from 1.5% to 2.4% while on SOF/VEL for 12 weeks, 16.1% among those who received SOF/VEL + RBV for 12 weeks; for those who received SOF + RBV for 12 weeks and SOF + RBV for 24 weeks, the rates were 1.5%, and 5.5%, respectively, and no patient who received placebo had any SAEs (Table 12).

[redacted]; among patients who received SOF+ RBV for 24 weeks, [redacted] but four SAEs led to premature discontinuation of study drug ([redacted]). In the ASTRAL-4 trial, hepatic encephalopathy, hyponatremia, and urinary tract infection were reported in two patients each, sepsis was reported in three patients, and no other SAE was reported in more than one patient.

3.7.3 Withdrawals due to adverse events

Few patients discontinued therapy due to AEs. Where the rates of discontinued therapy due to AEs ranged from [redacted] to [redacted] while on SOF/VEL for 12 weeks, 4.6% among those who received SOF/VEL + RBV for 12 weeks, while in those who received SOF + RBV for 12 weeks and SOF + RBV for 24 weeks, it was 0% and 3.3%, respectively, and in those who received placebo, two patients (1.7%) discontinued therapy due to adverse events (Table 12).

In ASTRAL-3, insomnia was the only AE leading to premature discontinuation of study drug reported in more than one patient among those who received SOF + RBV for 24 weeks. [redacted]

3.7.4 Mortality

In ASTRAL-1, one patient with chronic genotype 5 HCV infection died in the study. The patient completed 12 weeks of treatment with SOF/VEL without incident. The patient died while sleeping, eight days after treatment completion. The death was considered unrelated to study drug by the investigator. No death was reported in the placebo group.

In ASTRAL-2, two patients in the SOF/VEL for 12 weeks treatment group died in the study, and no death was reported in the SOF + RBV for 12 weeks treatment group. Of the patients who died, one of them was diagnosed with metastatic lung cancer [redacted] on post-treatment day 69 and died on post-treatment day 112. The SAEs were considered by the investigator not to be related to the study drug. While the other patient had an unwitnessed cardiac arrest in her home on post-treatment day 130 and died on post-treatment day 131. The SAE was considered by the investigator not to be related to the study drug.

In ASTRAL-3, no patient in the SOF/VEL for 12 weeks treatment group died, while three deaths were reported in the SOF + RBV for 24 weeks treatment group. Of the patients who died, one of them died of natural causes on day 141. Another patient died from multiple gunshot wounds on day 74. The third patient [redacted], he died of an unknown cause on post-treatment day 118. For all three deaths, the SAEs were assessed by the investigator not to be related to the study drug.

In ASTRAL-4, three patients in the SOF/VEL + RBV for 12 weeks treatment group died in the study: One patient died due to sepsis, another patient due to cardiopulmonary arrest secondary to end-stage liver disease, and the third patient died due to respiratory failure. For all three deaths, the SAE were assessed by the investigator not to be related to the study drug.

3.7.5 Notable harms

Patients treated with SOF/VEL for 12 weeks reported the occurrence of nausea ([redacted] fatigue ([redacted] pruritus ([redacted] headache ([redacted] and insomnia ([redacted]), while patients treated with SOF/VEL + RBV for 12 weeks reported nausea (25.3%), fatigue (39.1%), pruritus (4.6%), headache (20.7%), and insomnia (13.8%). AEs reported while on SOF + RBV for 12 weeks or SOF + RBV for 24 weeks included nausea (14.4% and 21.1%, respectively), fatigue (35.6% and 38.2%, respectively), pruritus ([redacted] respectively), headache (22% and 32.4%, respectively), and insomnia (13.6% and 26.9%, respectively) (Table 12).

Anemia, defined as a decline in hemoglobin to < 100 g/L, was reported in [redacted]. In ASTRAL-4, one patient in the SOF/VEL + RBV for 12 weeks treatment group received erythropoietin for anemia.

In all four trials, ALT > 5× ULN (upper limit of normal) was reported in [redacted], and 0% in patients who received SOF/VEL + RBV for 12 weeks, [redacted]. None of the patients receiving SOF/VEL for 12 weeks had hyperbilirubinemia > 5× ULN, one patient (0.4%) receiving SOF + RBV for 24 weeks, and [redacted]. Lipase elevation > 5× ULN was reported in [redacted] of patients receiving SOF/VEL for 12 weeks, 0.8% of patients receiving SOF + RBV for 12 weeks, 1.1% of patients receiving SOF + RBV for 24 weeks, and 0% among patients receiving SOF/VEL + RBV for 12 weeks or placebo (Table 12).

TABLE 12: HARMS

	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 weeks	PBO 12 weeks	SOF/VEL for 12 weeks	SOF + RBV for 12 weeks	SOF/VEL for 12 weeks	SOF + RBV for 24 weeks	SOF/VEL + RBV for 12 weeks
N	624	116	134	132	277	275	87
Any AE, n (%)	[redacted]	89 (76.7)	[redacted]	101 (76.5)	[redacted]	260 (94.5)	79 (90.8)
SAE, n (%)	[redacted]	0	[redacted]	2 (1.5)[a,b]	[redacted]	15 (5.5)[a,c]	14 (16.1)[d]
Death, n (%)	1 (0.2)	0	2 (1.5)	0	[redacted]	3 (1.1)	3 (3.4)
AE leading to discontinuation of study drug, n (%)	[redacted]	2 (1.7)	1 (0.7)	0	[redacted]	9 (3.3)	4 (4.6)[e]
Notable harms, n (%)							
Nausea	[redacted]	13 (11.2)	[redacted]	19 (14.4)	[redacted]	58 (21.1)	22 (25.3)
Fatigue	[redacted]	23 (19.8)	[redacted]	47 (35.6)	[redacted]	105 (38.2)	34 (39.1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (4.6)
Headache	[redacted]	33 (28.4)	[redacted]	29 (22.0)	[redacted]	89 (32.4)	18 (20.7)
Insomnia	[redacted]	11 (9.5)	[redacted]	18 (13.6)	[redacted]	74 (26.9)	12 (13.8)
ALT elevations, n (%)							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 2.5 to 5.0 ULN	[redacted]	[redacted]	[redacted]	3 (2.3)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 10.0 ULN	[redacted]	2 (1.7)	[redacted]	0	[redacted]	[redacted]	[redacted]
Hyperbilirubinemia, n (%)							
> 1.0 to 1.5 × ULN	[redacted]	10 (8.6)	[redacted]	26 (19.7)	[redacted]	[redacted]	[redacted]
> 1.5 to 2.5 × ULN	[redacted]	0	[redacted]	8 (6.1)	[redacted]	24 (8.7)	[redacted]
> 2.5 to 5.0 × ULN	[redacted]	0	[redacted]	3 (2.3)	[redacted]	2 (0.7)	20 (23.0)
> 5.0 × ULN	[redacted]	0	[redacted]	0	[redacted]	1 (0.4)	2 (2.3)
Anemia, n (%)							
Hemoglobin (100 g/L to 109 g/L)	[redacted]	1 (0.9)	[redacted]	45 (34.1)	[redacted]	[redacted]	[redacted]
Hemoglobin (90 g/L to < 100 g/L)	[redacted]	0	[redacted]	22 (16.7)	[redacted]	57 (20.7)	[redacted]
Hemoglobin (70 g/L to < 90 g/L)	[redacted]	0	[redacted]	7 (5.3)	[redacted]	25 (9.1)	10 (11.5)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipase elevations, n (%)							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 3.0 to 5.0 × ULN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2 (28.6)
> 5.0 × ULN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0

AE = adverse event; ALT = alanine aminotransferase; PBO = placebo; SAE = serious adverse event; SOF = sofosbuvir; ULN = upper limit of normal; VEL = velpatasvir.

[a] No SAE was reported in > 1 patient.

[b] No SAEs led to treatment discontinuation.

[c] A total of 4 SAEs led to premature discontinuation of study drug (cerebrovascular accident, intentional overdose, peripheral artery stenosis, and psychotic disorder).

[d] Hepatic encephalopathy, hyponatremia, and urinary tract infection occurred in 2 patients each; sepsis occurred in 3 patients. No other SAE was reported in > 1 patient.

[e] Adverse Event Leading to Premature Discontinuation of SOF/VEL.

Source: Feld et al.;[35] Foster et al.;[36] Curry et al.;[37] Clinical Study Reports: ASTRAL-1,[40] ASTRAL-2,[41] ASTRAL-3,[42] ASTRAL-4.[43]

4. DISCUSSION

4.1 Summary of available evidence

A total of four pivotal phase 3 clinical trials were included in this review (ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4). All trials were randomized and multi-centre. ASTRAL-1 was double blind, while ASTRAL-2, ASTRAL-3, and ASTRAL-4 were open label. ASTRAL-1 (N = 741) assessed the efficacy and safety of SOF/VEL for 12 weeks compared with placebo among treatment-naive and previously treated patients with chronic genotype 1, 2, 4, 5, or 6 HCV infection, including those with compensated cirrhosis. ASTRAL-2 (N = 269) assessed the efficacy and safety of 12 weeks of the SOF/VEL treatment compared with 12 weeks of SOF + RBV treatment in treatment-naive and previously treated patients with chronic genotype 2 HCV infection, including those with compensated cirrhosis. ASTRAL-3 (N = 558) assessed the efficacy and safety of 12 weeks of the SOF/VEL treatment compared with 24 weeks of SOF + RBV treatment in treatment-naive and previously treated patients with chronic genotype 3 HCV infection, including those with compensated cirrhosis. ASTRAL-4 (N = 268) assessed the efficacy and safety of SOF/VEL + RBV for 12 weeks in treatment-naive and previously treated patients with chronic genotypes 1 through 6 who had decompensated cirrhosis (classified as CTP class B).

The main outcome in the included trials was the proportion of patients achieving sustained virologic response at 12 weeks (SVR12). The main limitation of the ASTRAL-1 trial was the lack of an active treatment comparator arm consisting of an existing treatment regimen for CHC genotypes 1, 2, 4, 5 or 6 infection. Similarly, for the ASTRAL-4 trial, a main limitation was the lack of an active treatment comparator arm consisting of an existing treatment regimen for CHC. All included trials except ASTRAL-1 were open label; therefore, being aware of treatment allocation might have influenced subjective measures, such as HRQoL measures and reporting of AEs. The primary outcome of ASTRAL-1 compared SVR12 versus a performance goal, the reason for the choice of which was not clear; and the ASTRAL-4 trial compared the SVR12 rate versus a spontaneous rate of 1%, but currently there are other treatments indicated for patients with HCV who have with compensated and decompensated cirrhosis. In the ASTRAL-4 trial, there were limited data available in patients with genotypes 2 or 4 HCV, and no patients with genotypes 5 or 6 HCV were enrolled in the SOF/VEL + RBV treatment arm. Hence, there is uncertainty regarding the SVR for these genotypes.

4.2 Interpretation of results

4.2.1 Efficacy

The manufacturer is seeking reimbursement for SOF/VEL consistent with the Health Canada indication; i.e., in patients with chronic HCV infection with any genotype, without cirrhosis, with compensated cirrhosis, or with decompensated cirrhosis. In the patient group input received by CDR for this submission, patients' expectations were that the infection would be cured and that treatment options would be provided for patients who have failed standard therapy, those who have contraindications or cannot tolerate interferon, those coinfected with HIV, those with kidney impairment, those with compensated cirrhosis, and those infected with rare and/or multiple HCV genotypes. (See 0.)

In the ASTRAL-1 study, which included treatment-naive and previously treated patients with chronic genotype 1, 2, 4, 5, or 6 HCV infection, including those with compensated cirrhosis, the Health Canada–approved regimen of SOF/VEL for 12 weeks was associated with high rates of successful treatment: 99.0% (95% CI, 97.9% to 99.6%) of patients (618 of 624) achieved SVR12. This rate was statistically superior relative to the pre-specified performance goal of 85% ($P < 0.001$). In the ASTRAL-2 study, which included treatment-naive and previously treated patients with chronic genotype 2 HCV infection,

including those with compensated cirrhosis, the Health Canada–approved regimen of SOF/VEL for 12 weeks was associated with high rates of successful treatment: 99.3% (95% CI, 95.9% to 100%) of patients (133 of 134) achieved SVR12, while in the SOF + RBV for 12 weeks treatment group, 93.9% (95% CI, 88.4% to 97.3%) of patients (124 of 132) achieved SVR12. The 12-week regimen of SOF/VEL was statistically noninferior to SOF + RBV for 12 weeks, the primary end point of the study. Treatment with SOF/VEL for 12 weeks was shown to be statistically superior to SOF + RBV for 12 weeks, as demonstrated by the *P* value of 0.018. In the ASTRAL-3 study, which included treatment-naive and previously treated patients with chronic genotype 3 HCV infection, including those with compensated cirrhosis, the Health Canada–approved regimen of SOF/VEL for 12 weeks was associated with high rates of successful treatment: 95.3% (95% CI, 92.1% to 97.5%) of patients (264 of 277) achieved SVR12, while in the SOF + RBV for 24 weeks treatment group, 80.4% (95% CI, 75.2% to 84.9%) of patients (221 of 275) achieved SVR12. The strata-adjusted difference (95% CI) in the proportions was 14.8% (9.6% to 20.0%), demonstrating superiority of treatment with SOF/VEL for 12 weeks over SOF + RBV for 24 weeks for SVR12.

In the ASTRAL-1 study, the high SVR12 rate was seen in all subgroups of patients (patients with cirrhosis, without cirrhosis, with prior treatment failure, treatment-naive, and previously treated with a DAA + PR). The SVR12 rate was high among patients with genotype 1, 2, 4, 5, and 6 HCV infection. However, the number of patients with genotypes 5 and 6 treated with SOF/VEL was low (only 35 patients with genotype 5, and 41 with genotype 6 HCV), which limits the generalizability of results for these two genotypes. There were two virologic failures among 624 patients treated with SOF/VEL; both had genotype 1 HCV infection and both relapsed by post-treatment week 4. Baseline NS5A or NS5B RAVs had no impact on SVR12, with high SVR12 across all HCV genotypes and subtypes regardless of the presence of RAVs. In the ASTRAL-2 study, treatment with SOF/VEL for 12 weeks resulted in high SVR12 rates with no virologic failures in patients with genotype 2 HCV infection, irrespective of treatment status, cirrhosis, and presence of baseline NS5A RAVs. In the ASTRAL-3 study, despite a high combined SVR12 rate in the SOF/VEL for 12 weeks treatment group of 95%, both prior treatment-experienced (90.1% SVR, 64 of 71 patients) and cirrhosis (91.3% SVR, 73 of 80 patients) had a moderate negative impact on treatment responses. In the patient group with both cirrhosis and prior HCV treatment experience, the SVR12 rate was 89% (33/37). The SVR12 rates were 89.1% (57 of 64) in patients who had received a prior PR regimen, and 85.0% (17 of 20) in patients who were nonresponders to prior HCV treatment. In the SOF + RBV for 24 weeks treatment group, patients with cirrhosis had considerably lower SVR12 rates (55 of 83: 66.3%) than patients without cirrhosis (163 of 187: 87.2%), and patients with prior treatment experience had considerably lower SVR12 rates (45 of 71: 63.4%) than treatment-naive patients (176 of 204: 86.3%). In the ASTRAL-3 study, pre-treatment NS5A RAVs were present in [redacted] of patients, in the SOF/VEL for 12 weeks treatment group. There was a lower SVR12 rate in SOF/VEL-treated patients with baseline NS5A RAVs compared with patients without NS5A RAVs (88% vs. 97%, respectively). In the SOF/VEL for 12 weeks treatment group, the Y93H was detected in 25 (9%) of patients with an SVR12 rate of 84% (21/25). A total of 10 patients in the SOF/VEL for 12 weeks treatment group relapsed, and one patient was reinfected. All 10 patients had the NS5A RAV Y93H detected at relapse time points. It is unknown what the impact of NS5A is for other treatments for hepatitis C.

The ASTRAL-4 study included patients with genotype chronic genotypes 1, 2, 3, or 4 HCV infection who had decompensated cirrhosis. Manifestations of decompensated cirrhosis include the development of ascites, upper gastrointestinal bleeding secondary to varices or portal hypertensive gastropathy, jaundice, hepatic encephalopathy, liver cancer, renal failure, and sepsis. Once decompensated, the one-year mortality for patients with CTP class B decompensated cirrhosis is approximately 20%, while the

one-year mortality for patients with CTP class C decompensated cirrhosis is > 50%.[60,61] In this population with decompensated cirrhosis included in ASTRAL-4 study, the SVR12 rate for the SOF/VEL + RBV for 12 weeks treatment group was 94.3% (95% CI, 87.1% to 98.1%) of patients (82 of 87). SOF/VEL + RBV for 12 weeks treatment group met the primary efficacy end points with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%. Among patients with genotype 1 HCV infection, the SVR12 rate was 95.6% (65 of 68); among patients with genotype 3 HCV infection, the SVR12 rate was 84.6% (11 of 13). All patients with genotype 2 or 4 HCV infection achieved SVR12. Treatment with SOF/VEL + RBV for 12 weeks resulted in high SVR12 rates irrespective of genotype, prior treatment history, or baseline HCV RNA. However, the number of patients included was limited (four patients with genotype 2, two patients with genotype 4, and no patients with genotype 5 or 6); hence, the generalizability of the results for genotypes 2, 4, 5, or 6 is questionable. The presence of pre-treatment NS5A RAVs did not impact treatment outcome, while in genotype 1 HCV-infected patients, the SVR12 rates in patients with or without pre-treatment RAVs were similar in the SOF/VEL + RBV for 12 weeks treatment group. All patients with genotype 2 or 4 HCV infection achieved SVR12 irrespective of the presence of pre-treatment RAVs. Interpretation of the analyses of the impact of NS5A RAVs on treatment outcome in patients with genotype 3 HCV infection is limited by the small number of patients with NS5A RAVs. In the SOF/VEL + RBV for 12 weeks treatment group, three patients (one with genotype 1a and two with genotype 3a) experienced virologic failure. One patient with genotype 1a HCV infection had no NS5A or NS5B RAVs at failure. One patient with genotype 3a HCV infection had Y93H emerge at failure. Another patient with genotype 3a HCV infection had HCV with Y93H at pre-treatment and relapse, and also developed low levels of NS5B N142T+E237G at failure.

The ASTRAL-4 study assessed improvement in MELD and CTP scores. Eradication of chronic HCV in patients with decompensated liver disease provides a potential opportunity to reduce disease progression and possibly even reverse pre-existing disease. In a significant proportion of patients who achieved SVR12, regardless of treatment group, viral eradication was accompanied by a corresponding improvement in CTP and MELD scores in a high proportion of patients, where improvements in hepatic function, as indicated by reductions in CTP and MELD scores, were seen in a high proportion of patients (41 of 81 patients [50.6%] had improvement in MELD score; 33 of 81 patients [40.7%] had an improvement in CTP score). Twelve patients (14.8%) had no change in their MELD score, and 40 patients (49.4%) had no change in their CTP score. Improvements in MELD score were due largely to improvements in total bilirubin levels. Improvements in CTP score were largely due to improvements in albumin and bilirubin levels. Ten patients had MELD scores of 15 or more at baseline; these patients were most likely to have improvements in MELD, where [redacted] had improvement in MELD score, but this subgroup was small. There is no MCID for MELD score; hence, a decrease of 1 point in MELD score could be considered an improvement by physicians, while others would consider a decrease of at least 2 points an improvement. [redacted] Whether these changes in MELD and CTP scores will persist remains to be seen.

The CDR review protocol also included subgroup by HIV or hepatitis B coinfection, renal insufficiency, 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. Hence, the efficacy and safety of SOF/VEL in these subgroups of patients is still unknown.

Patient group input emphasized the impact that chronic hepatitis infection has on patients' quality of life. [redacted]

[redacted]

Results from the PROs for all four studies should be interpreted with caution as [redacted]. In addition, ASTRAL-2, ASTRAL-3, and ASTRAL-4 were open-label studies, and patients in ASTRAL-1 at 12 weeks after end of treatment became aware of what treatment they were on, which could bias the results in favour of the SOF/VEL regimen. 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 assesses whether mean ranks differ and differences in between-treatment groups with the corresponding 95% CI for the treatment difference were not estimated. Therefore, it is not possible to judge whether the difference between treatment groups is clinically meaningful. Finally, there is a lack of MCIDs specific to CHC, which is a problem for interpretation, and lack of validation in the CHC population for some measures, which could be a potential contributing factor to the inconsistencies in outcomes across the different measures.

Comparative efficacy data are limited due to the lack of an active comparator in the trials and lack of statistical comparisons between treatment arms. The manufacturer did not provide any indirect treatment comparisons in its submission. Despite the evolving standards for conducting a network meta-analysis with single-arm data, methodologies for using these data are available, and previous submissions for CHC treatments included indirect treatment comparisons that incorporated single-arm data.[62]

4.2.2 Harms

Patient group input described AEs associated with current pegylated interferon–based therapies as severe and debilitating. Hence, it is expected that pegylated interferon–free regimens such as SOF/VEL will be better tolerated than older regimens containing pegylated interferon. ASTRAL-1 compared SOF/VEL for 12 weeks with placebo. Treatment with SOF/VEL for 12 weeks was generally well tolerated, with a similar safety profile in the active and placebo treatment groups. There was a low incidence of SAEs in the SOF/VEL-treated patients and all SAEs were assessed by investigators as being not related to the study drug. Discontinuations for AEs were uncommon. The most common AEs were headache, fatigue, and nasopharyngitis in patients who received SOF/VEL for 12 weeks, while in those who received placebo for 12 weeks, it was headache, fatigue, and nausea.

In the ASTRAL-2 and ASTRAL-3 trials, treatment with SOF/VEL for 12 weeks was well tolerated in both trials and compared favourably to SOF + RBV for 12 weeks and SOF + RBV for 24 weeks, respectively. A smaller percentage of patients in the SOF/VEL for 12 weeks treatment groups experienced any AE compared with the SOF + RBV for 12 weeks and SOF + RBV for 24 weeks treatment groups, which were largely attributable to the higher rates of AEs typically associated with RBV, such as fatigue, headache, nausea, and insomnia. In the ASTRAL-2 trial, only [redacted] permanently discontinued the study drug (SOF/VEL) due to AEs after receiving one dose of SOF/VEL. In the ASTRAL-3 study, there were no discontinuations due to AEs in the SOF/VEL for 12 weeks treatment group compared with nine discontinuations due to AEs in the SOF + RBV for 24 weeks treatment group, suggesting that the more favourable safety and tolerability profile of the SOF/VEL for 12 weeks treatment group resulted in a higher rate of treatment completion.

In the ASTRAL-4 study, treatment with SOF/VEL + RBV was safe and well tolerated in this patient population with decompensated liver disease. As expected, given the underlying severity of liver disease in these patients, there was a higher percentage of patients experiencing AEs, SAEs, and AEs leading to discontinuation of study drug than observed in other studies in patients with compensated liver disease (studies ASTRAL-1, ASTRAL-2, and ASTRAL-3). A high percentage of patients in the SOF/VEL + RBV for 12 weeks treatment group experienced any AE (90.8%), primarily consistent with RBV-related toxicity. The most common AEs that occurred in > 10% of patients included fatigue, nausea, and anemia. The majority of SAEs observed were not treatment related. In total, there were three deaths in the study: One patient died due to sepsis, another patient due to cardiopulmonary arrest secondary to end-stage liver disease, and the third patient died due to respiratory failure. For all three deaths, the SAEs were assessed by the investigator as being not related to study drug. Consistent with RBV-associated hemolysis, there was a decrease in hemoglobin in the SOF/VEL + RBV for 12 weeks treatment group. Decreases in hemoglobin to < 100 g/L during treatment occurred in 24.1% (21 of 87) of patients in the SOF/VEL + RBV for 12 weeks treatment group.

5. CONCLUSIONS

Based on data from four pivotal phase 3 randomized clinical trials (one double-blinded placebo-controlled trial that also compared SVR12 versus a performance goal of 85%, two open-label trials that had active comparators, and one uncontrolled, open-label trial), SOF/VEL was associated with high rates of SVR12 in patients with genotype 1, 2, 3, 4, 5, and 6 CHC infection. High rates of SVR12 were observed across several subgroups of interest: In treatment-naive and previously treated patients, including those with compensated cirrhosis, as well as patients with chronic genotype 1, 2, 3, or 4 HCV infection who had decompensated cirrhosis. The SVR12 rate for SOF/VEL in ASTRAL-1 was statistically superior relative to the pre-specified performance goal of 85%. In ASTRAL-2, SOF/VEL for 12 weeks was shown to be statistically superior to SOF + RBV for 12 weeks in patients with genotype 2, and in the ASTRAL 3 study, SOF/VEL for 12 weeks was shown to be statistically superior to SOF + RBV for 24 weeks in patients with genotype 3. In decompensated cirrhosis (ASTRAL-4), the SVR12 rate for the SOF/VEL + RBV for 12 weeks treatment group was 94.3%, meeting the primary efficacy end points with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%. The data were limited for some populations in ASTRAL-4; specifically, patients with CHC genotype 2 or 4, and no patients with genotype 5 or 6 were enrolled. [redacted] SAEs and withdrawals due to AEs were very limited, indicating good tolerability of the evaluated medication. Characteristic AEs associated with pegylated IFN appeared to occur less frequently among patients treated with SOF/VEL. However, the relative efficacy and safety of SOF/VEL compared with more recent IFN-free HCV therapies is uncertain, due to the absence of direct or indirect comparative evaluations.

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(s) 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 fundraising and outreach efforts. The CLF has received unrestricted educational grants and/or has worked on joint initiatives with 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 Gastrointestinal (GI) Society is a Canadian leader in providing trusted, evidence-based information on all areas of the GI tract, and is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to health care, and promoting gastrointestinal and liver health. The GI Society receives financial contributions from pharmaceutical companies in support of its independent charitable work for Canadians affected by GI and liver conditions. In the last two years, the GI Society received funding from AbbVie Corporation, Actavis, AstraZeneca Canada Inc., Innovative Medicines Canada, Ferring Inc., Gilead Sciences Canada Inc., GlaxoSmithKline Inc., Janssen Canada, Merck Canada Inc., Pfizer Canada Inc., Shire Canada Inc., and Takeda Canada Inc. However, the GI Society declared no conflicts of interest in the preparation of this submission.

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization addressing access to treatment, care, and support for people living with HIV and hepatitis C. Full membership is limited to persons living with HIV/AIDS (including HCV coinfection) or organizations with a substantial HIV/AIDS mandate. CTAC received unrestricted organizational and/or educational grants from the following organizations in the 2014-2015 fiscal year: Abbott/AbbVie, Gilead Sciences Canada Inc., Janssen Inc., and ViiV Healthcare.

The Pacific Hepatitis C Network's mission is to strengthen the capacity of individuals and organizations throughout British Columbia to prevent new hepatitis C virus (HCV) infections and to improve the health and treatment outcomes of people already living with HCV. Its members include individuals at risk, exposed to, or concerned about HCV. The Pacific Hepatitis C Network has received project grants from AbbVie Corporation, Bristol-Myers Squibb, Gilead Science, Janssen Pharmaceuticals, and Merck Canada for online HCV treatment information resource. It declared no conflicts of interest in the preparation of this submission.

Hepatitis C Education and Prevention Society (HepCBC) is a non-profit organization run by and for people affected by HCV in British Columbia. It focuses on providing peer support groups, anti-stigma activities, prevention education, general hepatitis information, and encouraging testing among at-risk groups, among other activities. 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 and on buses (events and hepatitis C patient

awareness), and holding awareness activities from the following pharmaceutical companies over the last four years: Merck Pharmaceuticals, Lupin Pharmaceuticals, Vertex Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim, and AbbVie, plus support from Rx&D, the pharmaceutical umbrella organization.

2. Condition-related information

The information was gathered through interviews with patients and caregivers affected by hepatitis C, nurse specialists, gastroenterologists, hepatologists, and pharmacists, through surveys, meetings with support groups, and a webinar that included patients diagnosed with hepatitis C.

Hepatitis C is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), liver failure, and death. For those coinfected with HIV, liver disease progression may be exacerbated. Furthermore, coinfected patients express additional psychological, emotional, and physical distress, as many of their respective medications have an impact on one another. Some patients have few or no symptoms, but others experience fatigue; abdominal, muscle or joint pain; poor circulation; constipation; diarrhea; nausea; headaches; loss of appetite; sensitivity to light or food; portal hypertension; reflex impairment; psoriasis; peripheral neuropathy; osteopenia; disrupted sleep; and jaundice. The disease affects the cognitive functions of some patients, and they find it difficult to function when their thinking, memory, or focus is impeded. The fatigue and other symptoms may be severe and can limit patients' ability to work, manage their home, care for family members, and maintain friendships. According to patient groups, it was described as "a disease that affects all aspects of life before it may take it". The symptoms and impact of hepatitis C described by patients ranged from "have not had hep C symptoms" to "…five years of brutal pain and mental disability, liver transplant recovery, on and off 10 years, terrible nausea three times a week…" and "brain fog".

Patients must cope with the stigma associated with hepatitis C and are often reluctant to disclose their hepatitis C status for fear of rejection, discrimination, or ostracism. Marriages and other personal relationships often cannot survive the strain. To patients, a cure means freedom from debilitating fatigue and stigma-centred fear, and optimism about their health.

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

3. Current therapy-related information

The former standard therapy can be long and gruelling and usually involves weekly injections of pegylated interferon accompanied by ribavirin (six to eight pills per day) for up to 48 weeks. The adverse effects caused by the former standard therapies can be severe and debilitating, such as extreme fatigue, anemia, depression, anxiety, mood swings, rashes, insomnia, cognitive impairment, irritability, memory loss, headaches, hearing loss, chills, nausea, weight loss, suppressed appetite, hair loss, and joint pain. In addition, some therapy regimens require specific food requirements, and have adverse drug interactions with antiretroviral therapies (i.e., patients coinfected with HIV). The adverse effects of treatment may impact the patients' ability to continue working and to manage their households,

childcare, and relationships. In addition to the side effects with former standard therapy, patients have no way of knowing if the treatments will be successful and if their efforts to complete therapy will be worth it. Patients have also reported that the injections associated with interferon can be a triggering factor and a source of anxiety for those with a history of injection drug use. According to patient groups, the debilitation due to the adverse effects, regimen burden, tolerance, and success rate of the current standard therapy causes hepatitis C patients to delay treatment until necessary, or causes withdrawal from current treatment.

The side effects of former standard therapy for hepatitis C can leave patients completely dependent and unable to contribute financially, physically, or emotionally, and therefore the burden falls on the caregiver (often family) to compensate. Patient groups suggest that the burden extends beyond the direct caregiver and includes everyone in the HCV patient's social circle (family, friends, and coworkers) to help support them during treatment. For caregivers, 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. Patient groups identify the following roles and responsibilities for those giving care to patients with HCV infection: Education and counsel about currently available treatment options and management medical appointments and drug regimens. Caregivers also identify some of the consequences associated with the debilitation of patients caused by HCV treatments. These include depression, increased family obligations, financial worries, social isolation, lack of social support, absenteeism from work, increased household responsibilities, stress, tiredness, resentment, and guilt. In addition, patient groups have also expressed the concerns of caregivers with respect to the possibility of HCV infection. Caregivers continuously emphasize their helplessness with respect to the health and future of hepatitis C patients, as well as the need for new treatment options to reduce the hardships of treatment failure and/or ineligibility. Many patients have contraindications or cannot tolerate interferon and thus are ineligible for interferon-based regimens. Those who have failed interferon-based treatments have few treatment options. Patient groups mention optimism and excitement about novel interferon-free direct-acting antivirals agents (DAAs) for HCV treatment, especially for those patients who are hard to treat. These patients include those who have failed standard therapy, those who have contraindications to or who cannot tolerate interferon, those coinfected with HIV, those with kidney impairment, those with compensated cirrhosis, and those infected with rare and/or multiple HCV genotypes.

Patients undergoing treatment with DAAs such as the elbasvir plus grazoprevir combination and sofosbuvir plus ledipasvir (Harvoni) may take a single tablet each day.

4. Expectations about the drug being reviewed

According to patient groups (including patients' experience with sofosbuvir plus velpatasvir [SOF/VEL] reported by their physicians and the experience with SOF/VEL reported directly by one patient), the general expectations of novel HCV infection treatments are that they will reduce suffering (adverse events and regimen burden), encourage interferon-free oral DAA regimens, and provide for greater treatment success rates (i.e., sustained virologic response [SVR]) and shorter treatment regimens. Patients suggest that if these expectations are met, it would translate to less hardship (requiring less mental and physical support) and would result in improved treatment adherence. SOF/VEL is an IFN-free DAA that received a Health Canada indication for the treatment of chronic HCV infection in adults for all genotypes on July 11, 2016. SOF/VEL is the first therapy that offers a high cure rate across all genotypes (1 to 6) with only mild side effects (headache, fatigue, nausea). Many patients taking this therapy as part of clinical trials were convinced that they were taking a placebo because they experienced almost no side effects. The regimen requires one pill a day for as few as 12 weeks and has no stringent food

requirements. No dosage adjustments are needed. A physician treating hepatitis C patients said, "Excellent experience across the board. One pill a day — doesn't get much easier. Much, much, much easier than interferon-based therapy. Many asked if they were on placebo!" Ultimately, hepatitis C patients, regardless of genotype, are looking for a safe, effective, affordable, and easy-to-take therapy that will cure their hepatitis C and allow them to reclaim their lives.

The expectations for SOF/VEL are that it will address the gap in treatment and unmet needs of hepatitis C patients, such as null response or relapse patients, those who have contraindications to or who cannot tolerate interferon, those coinfected with HIV, those with liver impairment, those with compensated or decompensated cirrhosis, and those infected with rare and/or multiple HCV genotypes. Patients also have high expectations of a cure with SOF/VEL. Once cured, they expect that their fibrosis and/or cirrhosis will reverse, and their risk of end-stage liver disease will be reduced. Patients state that they are looking to receive treatment as early as possible, regardless of their disease status. The accessibility and affordability with SOF/VEL is of great concern to HCV patients.

Patients were encouraged about the availability of this drug for the following reasons: the treatment has overall high SVR, reduced adverse effects, reduced regimen burden, and it is IFN-free. Moreover, currently available treatment options are limited. Additionally, patients are also pleased with the short treatment time frame, further minimizing potential side effects and the chances of inadvertently spreading the disease. Decreasing treatment time is a priority for patients and health care providers because of its impact on treatment adherence and side effects, and on expediting patients' return to their normal lives. Patient groups report that personal and professional relationships will improve and the stigma of the disease will decrease if SOF/VEL is accessible and affordable. Based on feedback from treatment-experienced individuals, SOF/VEL was easy to administer and tolerate.

Several respondents suggested that clinical trials are looking to improve subsequent generations of DAAs over previous ones, but regretted that ribavirin, and occasionally interferon, were still being used or reviewed in newer treatments. As one caretaker respondent reported, "Living with someone who is taking interferon and ribavirin can be extremely challenging." These requirements are frustrating for individuals, "especially those who are experiencing multiple barriers, to be told that they are not sick enough to start treatment." SOF/VEL offers hope to patients who are infected to any degree across HCV genotypes 1 to 6, as well as those who failed previous treatments and those with genes that have been associated with a poor response to interferon therapy. This is a remarkable opportunity to eradicate the virus from many high-risk individuals in Canada, as well as from the population at large and to prevent further spread of a malevolent infectious disease that has no vaccine. A SOF/VEL-experienced patient said that SOF/VEL does "offer a choice, but the price must be comparable to Harvoni, or I see no value in this product." One patient group pointed out that the biggest barrier to treatment with the new DAA combinations is their high cost, which has led to insurers and governments rationing these cures.

HepCBC noted the recent investigation by the European Medicines Agency (EMA) into the possibility of hepatitis B virus (HBV) reactivation among HCV patients taking the new IFN-free DAA treatments. They indicated that it is prudent to suggest that all HCV patients who are about to embark on an all-oral regime have their HBV status confirmed prior to starting treatment; at least until the EMA investigation provides more data. HepCBC also noted that research has indicated a possible recurrence of liver cancer following (third-generation) DAA treatment. HCC is a factor that must be considered carefully before a treatment regimen is prescribed, at least until more data become available.

5. Additional information

It appears that SOF/VEL may be the "one-pill-fits-all" therapy for all patients. Patient groups therefore call upon the CADTH Canadian Drug Expert Committee to recommend reimbursement for SOF/VEL for all genotypes of hepatitis C. Patients are concerned that the prices of SOF/VEL will be high, like other drugs in its class, and that it will not get approved, or that the coverage criteria will require patients to undergo and fail very challenging standard treatments (with both interferon and ribavirin) before treatment access to SOF/VEL is granted. Patients, especially those who are experiencing multiple barriers, find it frustrating to be told that they are not sick enough to qualify for treatment. Patients worry about the liver damage that may be caused by delaying treatment. The sooner a person is effectively treated (i.e., cured), the less chance they have of inadvertently infecting someone else. Patients note that all those infected with HCV are not homogenous and cannot be treated as such. Customized treatments are necessary to achieve the best possible outcomes based on patient needs, and would require more treatment options to be accessible. Improved treatments for hepatitis C have the potential to reduce social system and health care costs for patients with severe liver disease. All patient groups would prefer that this treatment is offered to all people with HCV, regardless of the patients' severity of liver damage.

Patients groups believe that SOF/VEL, with its ability to cure multiple HCV genotypes and "hard-to-treat" patients, as well as the fact that it results in fewer side effects than other treatments, will help Canada succeed in helping to cure Canadians living with hepatitis C.

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:	May 24, 2016
Alerts:	Bi-weekly search updates until September 21 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
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	Requires words are adjacent to each other (in any order)
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	
Line #	**Search Strategy**
1	("Sofosbuvir/velpatasvir" or S900007160).ti,ab,kf,ot,hw,rn,nm.
2	(Sofosbuvir* or sovaldi* or HSDB 8226 or GI 7977 or GI7977 or GS-7977 or GS7977 or PSI 7977 or PSI7977or WJ6CA3ZU8B or 1190307-88-0).ti,ab,kf,ot,hw,rn,nm.
3	(1190307-88-0 or WJ6CA3ZU8B).rn,nm.
4	2 or 3
5	(Velpatasvir* or GS5816 or GS 5816).ti,ab,kf,ot,hw,rn,nm.
6	(1377049-84-7 or 1458063-71-2 or KCU0C7RS7Z).rn,nm.
7	5 or 6
8	4 and 7
9	1 or 8
10	9 use pmez
11	*sofosbuvir plus velpatasvir/
12	("Sofosbuvir/velpatasvir" or S900007160).ti,ab,kw.
13	11 or 12
14	*sofosbuvir/
15	(Sovaldi* or sofosbuvir* or GI 7977 or GI7977 or GS-7977 or GS7977 or PSI 7977 or PSI7977).ti,ab,kw.
16	14 or 15
17	*velpatasvir/
18	(Velpatasvir* or GS5816 or GS 5816).ti,ab,kw.
19	17 or 18
20	16 and 19
21	13 or 20
22	21 use oemezd
23	conference abstract.pt.
24	22 not 23
25	10 or 24
26	remove duplicates from 25

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:	May 2016
Keywords:	Velpatasvir, sofosbuvir
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
- Clinical Trials
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

There were no excluded studies.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 13: SUMMARY OF SUSTAINED VIROLOGIC RESPONSE IN ASTRAL-1

	ASTRAL-1							
	SOF/VEL for 12 weeks							
	Total (All Genotypes) (N = 624)	**GT1a (N = 210)**	**GT1b (N = 118)**	**GT1 Total (N = 328)**	**GT2 (N = 104)**	**GT4 (N = 116)**	**GT5 (N = 35)**	**GT6 (N = 41)**
SVR12 (Full Analysis Set)								
N (%) [95% CI]	618 (99) [97.9 to 99.6]	[redacted]	[redacted]	323 (98.5) [96.5 to 99.5]	104 (100.0) [96.5 to 100.0]	116 (100.0) [96.9 to 100.0]	34 (97.1) [85.1 to 99.9]	41 (100.0) [91.4 to 100.0]
P value (compared with 85%)	< 0.001							
Overall virologic failure, n/N (%)	2/624 (0.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	2/623 (0.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On-treatment virologic failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Did not achieve SVR for other reasons	4/624 (0.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SVR by Cirrhosis, n/N (%) [95% CI]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ASTRAL-1							
	SOF/VEL for 12 weeks							
	Total (All Genotypes) (N = 624)	**GT1a (N = 210)**	**GT1b (N = 118)**	**GT1 Total (N = 328)**	**GT2 (N = 104)**	**GT4 (N = 116)**	**GT5 (N = 35)**	**GT6 (N = 41)**
Missing	2/2 (100.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline HCV RNA (IU/mL), n/N (%) [95% CI]								
< 800,000	[redacted]	[redacted]	[redacted]	72/73 (98.6)	29/29 (100.0)	42/42 (100.0)	8/9 (88.9)	10/10 (100.0)
≥ 800,000	[redacted]	[redacted]	[redacted]	251/255 (98.4)	75/75 (100.0)	74/74 (100.0)	26/26 (100.0)	31/31 (100.0)
Prior HCV Treatment Experience, n/N (%) [95% CI]								
Treatment-naïve	418/423 (98.8)	128/132 (97.0)	86/86 (100.0)	214/218 (98.2)	79/79 (100.0)	64/64 (100.0)	23/24 (95.8)	38/38 (100.0)
Treatment-experienced	200/201 (99.5)	78/78 (100.0)	31/32 (96.9)	109/110 (99.1)	25/25 (100.0)	52/52 (100.0)	11/11 (100.0)	3/3 (100.0)
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ASTRAL-1							
	SOF/VEL for 12 weeks							
	Total (All Genotypes) (N = 624)	GT1a (N = 210)	GT1b (N = 118)	GT1 Total (N = 328)	GT2 (N = 104)	GT4 (N = 116)	GT5 (N = 35)	GT6 (N = 41)
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

CI = confidence interval; DAA = direct-acting antiviral; GT = genotype; HCV = hepatitis C virus; peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR = sustained virologic response; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Source: Feld et al.;[35] Clinical Study Reports: ASTRAL-1.[40]

TABLE 14: SUMMARY OF SUSTAINED VIROLOGIC RESPONSE IN ASTRAL-2 AND ASTRAL-3

	ASTRAL-2		ASTRAL-3	
	SOF/VEL 12 Weeks (N = 134)	SOF + RBV 12 Weeks (N = 132)	SOF/VEL 12 Weeks (N = 277)	SOF + RBV 24 Weeks (N = 275)
SVR12 (Full Analysis Set)				
N (%) [95% CI]	133/134 (99.3) [95.9 to 100.0]	124/132 (93.9) [88.4 to 97.3]	264/277 (95.3) [92.1 to 97.5]	221/275 (80.4) [75.2 to 84.9]
Difference (95% CI)	5.2 (0.2 to 10.3)		14.8 (9.6 to 20.0)	
P Value	0.018		< 0.001	
Overall virologic failure, n/N (%)	0/134	6/132 (4.5)	11/277 (4.0)	39/275 (14.2)
Relapse	0/133	6/132 (4.5)	11/276 (4.0)	38/272 (14.0)
On-treatment virologic failure	0/134	0/132	0/277	1/275 (0.4)

	ASTRAL-2		ASTRAL-3	
	SOF/VEL 12 Weeks (N = 134)	**SOF + RBV 12 Weeks (N = 132)**	**SOF/VEL 12 Weeks (N = 277)**	**SOF + RBV 24 Weeks (N = 275)**
Did not achieve SVR for other reasons	1/134 (0.7)	2/132 (1.5)	2/277 (0.7)	15/275 (5.5)
SVR by Cirrhosis				
Yes, n/N (%) [95% CI]	19/19 (100.0) [redacted]	18/19 (94.7) [redacted]	73/80 (91.3) [redacted]	55/83 (66.3) [redacted]
Difference (95% CI)	5.3 (–13.2 to 26.0)		25.0 (11.5 to 37.2)	
No, n/N (%) [95% CI]	114/115 (99.1) [redacted]	105/112 (93.8) [redacted]	191/197 (97.0) [redacted]	163/187 (87.2) [redacted]
Difference (95% CI)	5.4 (0.5 to 11.6)		9.8 (4.2 to 15.7)	
Missing, N (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
SVR by Baseline HCV RNA (IU/mL) , N (%) [95% CI]				
< 800,000, n/N (%) [95% CI]	23/23 (100.0) [redacted]	30/31 (96.8) [redacted]	85/86 (98.8) [redacted]	72/81 (88.9) [redacted]
Difference (95% CI)	3.2 (–11.5 to 17.4)		9.9 (2.8 to 18.9)	
≥ 800,000, n/N (%) [95% CI]	110/111 (99.1) [redacted]	94/101 (93.1) [redacted]	179/191 (93.7) [redacted]	149/194 (76.8) [redacted]
Difference (95% CI)	6.0 (0.8 to 12.8)		16.9 (9.9 to 24.0)	
SVR by Prior HCV Treatment Experience, N (%) [95% CI]				
Treatment-naive, n/N (%) [95% CI]	114/115 (99.1) [redacted]	107/112 (95.5) [redacted]	200/206 (97.1) [redacted]	176/204 (86.3) [redacted]
Difference (95% CI)	3.6 (–0.9 to 9.2)		10.8 (5.3 to 16.5)	
Cirrhosis: Yes			40/43 (93.0)	33/45 (73.3)
Cirrhosis: No			160/163 (98.2)	141/156 (90.4)
Cirrhosis: Missing			0	2/3 (66.7)
Treatment-experienced, n/N (%) [95% CI]	19/19 (100.0) [redacted]	17/20 (85.0) [redacted]	64/71 (90.1) [redacted]	45/71 (63.4) [redacted]
Difference (95%CI)	15.0 (–4.1 to 37.9)		26.8 (12.2 to 40.1)	
Cirrhosis: Yes			33/37 (89.2)	22/38 (57.9)
Cirrhosis: No			31/34 (91.2)	22/31 (71.0)
Cirrhosis: Missing			0	1/2 (50.0)
SVR by Prior HCV Treatment, N (%) [95% CI]				
DAA + peg-IFN + RBV, n/N (%) [95% CI]	[redacted]	[redacted]	1/1 (100.0) [redacted]	0/0

	ASTRAL-2		ASTRAL-3	
	SOF/VEL 12 Weeks (N = 134)	**SOF + RBV 12 Weeks (N = 132)**	**SOF/VEL 12 Weeks (N = 277)**	**SOF + RBV 24 Weeks (N = 275)**
Peg-IFN + RBV, n/N (%) [95% CI]	[redacted]	[redacted]	57/64 (89.1) [redacted]	41/65 (63.1) [redacted]
Difference (95% CI)	[redacted]		26.0 (9.8 to 40.3)	
Other, n/N (%) [95% CI]	[redacted]	[redacted]	6/6 (100.0) [redacted]	4/6 (66.7) [redacted]
Difference (95% CI)	[redacted]		33.3 (−17.4 to 77.7)	
SVR by Prior HCV Treatment Response, N (%) [95% CI]				
Nonresponder, n/N (%) [95% CI]	3/3 (100.0) [redacted]	2/3 (66.7) [redacted]	17/20 (85.0) [redacted]	14/24 (58.3) [redacted]
Difference (95% CI)	[redacted]		26.7 (−1.2 to 51.8)	
Relapse/breakthrough, n/N (%) [95% CI]	16/16 (100.0) [redacted]	15/17 (88.2) [redacted]	47/51 (92.2) [redacted]	31/47 (66.0) [redacted]
Difference (95% CI)	[redacted]		26.2 (8.9 to 42.5)	

CI = confidence interval; DAA = direct-acting antiviral; HCV = hepatitis C virus; SOF = sofosbuvir; peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SVR = sustained virologic response; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Source: Foster et al.;[36] Clinical Study Reports: ASTRAL-2,[41] ASTRAL-3.[42]

TABLE 15: SUMMARY OF SUSTAINED VIROLOGIC RESPONSE IN ASTRAL-4

	ASTRAL-4							
	SOF/VEL + RBV for 12 Weeks							
	Total (All Genotypes) (N = 87)	**GT1a (N = 54)**	**GT1b (N = 14)**	**GT1 Total (N = 68)**	**GT2 (N = 4)**	**GT3 (N = 13)**	**GT4 (N = 2)**	**GT6 (N = 0)**
SVR12 (Full Analysis Set)								
N (%) [95% CI]	82/87 (94.3) [87.1 to 98.1]	51/54 (94.4) [84.6 to 98.8]	14/14 (100.0) [76.8 to 100.0]	65/68 (95.6) [87.6 to 99.1]	4/4 (100.0) [39.8 to 100.0]	11/13 (84.6) [54.6 to 98.1]	2/2 (100.0) [15.8 to 100.0]	0
Overall Virologic Failure, n/N (%)	3/87 (3.4)	1/54 (1.9)	0/14	1/68 (1.5)	0/4	2/13 (15.4)	0/2	0
Relapse	2/85 (2.4)	1/53 (1.9)	0/14	1/67 (1.5)	0/4	1/12 (8.3)	0/2	0
On-treatment virologic failure	1/87 (1.1)	0/54	0/14	0/68	0/4	1/13 (7.7)	0/2	0
Did not achieve SVR for other reasons	2/87 (2.3)	2/54 (3.7)	0/14	2/68 (2.9)	0/4	0/13	0/2	0
SVR by Baseline HCV RNA (IU/mL), N (%) [95% CI]								
< 800,000, n/N (%) [95% CI]	40/42 (95.2) [83.8 to 99.4]	[redacted]	[redacted]	31/31 (100.0) [88.8 to 100.0]	[redacted]	3/5 (60.0) [14.7 to 94.7]	[redacted]	0
≥ 800,000, n/N (%) [95% CI]	42/45 (93.3) [81.7 to 98.6]	[redacted]	[redacted]	34/37 (91.9) [78.1 to 98.3]	[redacted]	8/8 (100.0) [63.1 to 100.0]	[redacted]	0
SVR by Prior HCV Treatment Experience, N (%) [95% CI]								
Treatment-naive, n/N (%) [95% CI]	36/40 (90.0) [76.3 to 97.2]	[redacted]	[redacted]	25/27 (92.6) [75.7 to 99.1]	[redacted]	8/10 (80.0) [44.4 to 97.5]	[redacted]	0
Treatment-experienced, n/N (%) [95% CI]	46/47 (97.9) [88.7 to 99.9]	[redacted]	[redacted]	40/41 (97.6) [87.1 to 99.9]	[redacted]	3/3 (100.0) [29.2 to 100.0]	[redacted]	0

	ASTRAL-4							
	SOF/VEL + RBV for 12 Weeks							
	Total (All Genotypes) (N = 87)	**GT1a (N = 54)**	**GT1b (N = 14)**	**GT1 Total (N = 68)**	**GT2 (N = 4)**	**GT3 (N = 13)**	**GT4 (N = 2)**	**GT6 (N = 0)**
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
SVR by Baseline CTP Score								
Baseline CTP score CTP A [5 to 6], n/N (%) [95% CI]	6/6 (100.0) [54.1 to 100.0]	[redacted]	[redacted]	4/4 (100.0) [39.8 to 100.0]	[redacted]	2/2 (100.0) [15.8 to 100.0]	[redacted]	0
Baseline CTP score CTP B [7 to 9], n/N (%) [95% CI]	72/77 (93.5) [85.5 to 97.9]	[redacted]	[redacted]	59/62 (95.2) [86.5 to 99.0]	[redacted]	8/10 (80.0) [44.4 to 97.5]	[redacted]	0

	ASTRAL-4							
	SOF/VEL + RBV for 12 Weeks							
	Total (All Genotypes) (N = 87)	**GT1a (N = 54)**	**GT1b (N = 14)**	**GT1 Total (N = 68)**	**GT2 (N = 4)**	**GT3 (N = 13)**	**GT4 (N = 2)**	**GT6 (N = 0)**
Baseline CTP score CTP C [10 to 12], n/N (%) [95% CI]	4/4 (100.0) [39.8 to 100.0]	[redacted]	[redacted]	2/2 (100.0) [15.8 to 100.0]	[redacted]	1/1 (100.0) [2.5 to 100.0]	[redacted]	0
SVR by Baseline MELD Score								
Baseline MELD score < 10, n/N (%) [95% CI]	29/29 (100.0) [88.1 to 100.0]	[redacted]	[redacted]	21/21 (100.0) [83.9 to 100.0]	[redacted]	5/5 (100.0) [47.8 to 100.0]	[redacted]	0
Baseline MELD score 10 to 15, n/N (%) [95% CI]	49/54 (90.7) [79.7 to 96.9]	[redacted]	[redacted]	41/44 (93.2) [81.3 to 98.6]	[redacted]	6/8 (75.0) [34.9 to 96.8]	[redacted]	0
Baseline MELD score 16 to 20, n/N (%) [95% CI]	4/4 (100.0) [39.8 to 100.0]	[redacted]	[redacted]	3/3 (100.0) [29.2 to 100.0]	[redacted]	0/0	[redacted]	0
Baseline MELD score 21 to 25, n/N (%) [95% CI]	0/0	[redacted]	[redacted]	0/0	[redacted]	0/0	[redacted]	0
[redacted]								
[redacted]				[redacted]		[redacted]		
[redacted]				[redacted]		[redacted]		
[redacted]				[redacted]		[redacted]		
[redacted]				[redacted]		[redacted]		
[redacted]				[redacted]		[redacted]		

	ASTRAL-4							
	SOF/VEL + RBV for 12 Weeks							
	Total (All Genotypes) (N = 87)	GT1a (N = 54)	GT1b (N = 14)	GT1 Total (N = 68)	GT2 (N = 4)	GT3 (N = 13)	GT4 (N = 2)	GT6 (N = 0)
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

CI = confidence interval; CTP = Child–Turcotte–Pugh; DAA = direct-acting antiviral; GT = genotype; HCV = hepatitis C virus; MELD = Model for End-Stage Liver Disease; peg-IFN = pegylated interferon; RAV = resistance-associated variant; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR = sustained virologic response; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Source: Curry et al.;[37] Clinical Study Reports: ASTRAL-4.[43]

TABLE 16: PREVALENCE OF BASELINE NS5A RESISTANCE-ASSOCIATED VARIANTS AND SVR12 RATES IN ASTRAL-1

	ASTRAL-1							
	SOF/VEL for 12 Weeks							
	GT1a (and Non-1b) (N = 208)	GT1b (N = 117)	GT2a (and Non-2b) (N = 61)	GT2b (N = 40)	GT4 (N = 116)	GT5 (N = 34)	GT6 (N = 43)	TOTAL (N = 619)
Patients with baseline NS5A deep sequence data, n	208	117	60	40	115	34	42	616
Patients with baseline NS5A RAVs, n/N (%)	50/208 (24)	25/117 (21)	60/60 (100)	22/40 (55)	72/115 (63)	6/34 (18)	22/42 (52)	257/616 (42)
SVR12 in patients with any	48/50 (96)	25/25 (100)	60/60 (100)	22/22 (100)	72/72 (100)	6/6 (100)	22/22 (100)	255/257 (99)

	ASTRAL-1							
	SOF/VEL for 12 Weeks							
	GT1a (and Non-1b) (N = 208)	GT1b (N = 117)	GT2a (and Non-2b) (N = 61)	GT2b (N = 40)	GT4 (N = 116)	GT5 (N = 34)	GT6 (N = 43)	TOTAL (N = 619)
NS5A RAVs, n/N (%)								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SVR12 in patients without NS5A RAVs, n/N (%)	158/158 (100)	92/92 (100)	NA	18/18 (100)	43/43 (100)	28/28 (100)	20/20 (100)	359/359 (100)

GT = genotype; NS5A = nonstructural protein 5A; RAV = resistance-associated variant; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Source: Clinical Study Reports: ASTRAL-1;[40]

TABLE 17: PREVALENCE OF BASELINE NS5A RESISTANCE-ASSOCIATED VARIANTS AND SVR12 RATES IN ASTRAL-2

	ASTRAL-2			
	SOF/VEL for 12 weeks			
	GT1a (N = 1)	GT2a (and Non-2b) (N = 25)	GT2b (N = 107)	TOTAL (N = 133)
Patients with pre-treatment NS5A deep sequence data, n	1	25	107	133
Patients with pre-treatment NS5A RAVs, n/N (%)	0	25 (100)	55 (51)	80 (60)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SVR12 in patients without NS5A RAVs, n/N (%)	1/1 (100)	NA	52/52 (100)	53/53 (100)

GT = genotype; NS5A = nonstructural protein 5A; RAV = resistance-associated variant; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Source: Clinical Study Reports: ASTRAL-2;[41]

TABLE 18: PREVALENCE OF BASELINE NS5A RESISTANCE-ASSOCIATED VARIANTS AND SVR12 RATES IN ASTRAL-3

	ASTRAL-2
	SOF/VEL for 12 weeks (N = 275)
Patients with baseline NS5A deep sequence data, n	274
Patients with baseline NS5A RAVs, n/N (% prevalence)	43/274 (16%)
SVR12 in patients with NS5A RAVs, n/N (%)	38/43[a] (88%)
[redacted]	[redacted]

NS5A = nonstructural protein 5A; RAV = resistance-associated variant; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.

[redacted]

Source: Clinical Study Reports: ASTRAL-3.[42]

TABLE 19: CHARACTERISTICS OF PATIENTS RECEIVING SOFOBUVIR/VELPATASVIR WHO RELAPSED IN ASTRAL-3

ASTRAL-3							
SOF/VEL for 12 Weeks							
HCV GT	Cirrhosis	HCV Treatment History	Timing of Virologic Failure	RAVs			
				NS5A		NS5B	
				Baseline NS5A RAV (%)	Virologic Failure NS5A RAV (%)	Baseline NS5B RAV	Virologic Failure NS5B RAV
3a	Yes	Naive	[redacted]	Y93H (15.2%)	Y93H (> 99%)	None	None
3a	Yes	Experienced	[redacted]	None	Y93H (> 99%)	None	None
3a	Yes	Naive	[redacted]	Y93H (> 99%)	Y93H (> 99%)	None	None
3a	No	Experienced	[redacted]	None	Y93H (> 99%)	None	None
3a	No	Naive	[redacted]	Y93H (> 99%)	Y93H (> 99%)	None	None
3a	Yes	Experienced	[redacted]	None	Y93H (> 99%)	None	None
3	No	Experienced	[redacted]	Y93H (2.8%)	Y93H (> 99%)	None	None
3a	Yes	Experienced	[redacted]	A30K (> 99%)	A30K (> 99%) Y93H (97.2%)	None	None
3a	Yes	Naive	[redacted]	None	Y93H (> 99%)	None	None
3a	Yes	Experienced	[redacted]	None	Y93H (> 99%)	None	None
3a	No	Experienced	[redacted]	None	GT1a reinfection		

GT = genotype; HCV = hepatitis C virus; RAV = resistance-associated variant; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir.
Source: Foster et al.;[36] Clinical Study Reports: ASTRAL-3.[42]

TABLE 20: PREVALENCE OF BASELINE NS5A RESISTANCE-ASSOCIATED VARIANTS AND SVR12 RATES IN ASTRAL-4

	ASTRAL-4					
	SOF/VEL + RBV for 12 weeks					
	GT1	GT2	GT3	GT4	GT6	Total
Patients with pre-treatment NS5A deep sequence data, n	66	4	13	2	NA	85
Patients with pre-treatment NS5A RAVs, n/N (%)	19/66 (29)	3/4 (75)	2/13 (15)	1/2 (50)	NA	25/85 (29)
SVR12 in patients with any NS5A RAVs, n/N (%)	19/19 (100)	[redacted]	1/2 (50)	[redacted]	NA	24/25 (96)
SVR12 in patients without NS5A RAVs, n/N (%)	46/47 (98)	[redacted]	10/11 (91)	[redacted]	NA	58/60 (97)

GT = genotype; NA = not applicable; RAV = resistance-associated variant; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Source: Clinical Study Reports: ASTRAL-4.[43]

TABLE 21: MELD CHANGE FROM BASELINE TO POST-TREATMENT VISITS, NUMBER (%) OF PATIENTS WITH EACH CHANGE VALUE FOR PATIENTS WHO ACHIEVED SVR12 IN ASTRAL-4

MELD Change From Baseline at Post-Treatment Week 12	ASTRAL-4		
	SOF/VEL + RBV for 12 Weeks (N = 82)		
	Baseline MELD Score		
	< 15 (N = 72)	≥ 15 (N = 10)	All Patients
–11	0/71	0/10	Decrease (improvement) = 41/81 (50.6)
–8	0/71	1/10 (10.0)	
–7	0/71	0/10	
–6	2/71 (2.8)	0/10	
–5	2/71 (2.8)	0/10	
–4	1/71 (1.4)	1/10 (10.0)	
–3	4/71 (5.6)	2/10 (20.0)	
–2	10/71 (14.1)	0/10	
–1	15/71 (21.1)	3/10 (30.0)	
0	10/71 (14.1)	2/10 (20.0)	No change = 12/81 (14.8)
1	12/71 (16.9)	0/10	[redacted]
2	11/71 (15.5)	0/10	
3	0/71	1/10 (10.0)	
4	3/71 (4.2)	0/10	
7	0/71	0/10	
11	1/71 (1.4)	0/10	
No assessment	1	0	No assessment = 1

MELD = Model for End-Stage Liver Disease; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Note: Baseline value is the last available value on or prior to first dose date of any study drug.
Source: Clinical Study Reports: ASTRAL-4.[43]

TABLE 22: SHIFTS IN MELD SCORE (< 15 OR ≥ 15) FROM BASELINE TO POST-TREATMENT WEEK 12 FOR PATIENTS WHO ACHIEVED SVR12 IN ASTRAL-4

	ASTRAL-4		
	SOF/VEL + RBV for 12 weeks		
	Post-Treatment Week 12 MELD Score		
Baseline MELD Score	< 15	≥ 15	No Assessment
< 15	68/71 (95.8)	3/71 (4.2)	1
≥ 15	4/10 (40.0)	6/10 (60.0)	0

MELD = Model for End-Stage Liver Disease; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Source: Clinical Study Reports: ASTRAL-4.[43]

TABLE 23: COMPONENTS OF MELD FOR PATIENTS WITH IMPROVEMENT IN MELD SCORE BETWEEN BASELINE AND POST-TREATMENT VISITS FOR PATIENTS WHO ACHIEVED SVR12 IN ASTRAL-4

	ASTRAL-4		
	SOF/VEL + RBV for 12 weeks		
	Bilirubin (mg/dL)	Creatinine (mg/dL)	INR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

INR = international normalized ratio; MELD = Model for End-Stage Liver Disease; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Note: Baseline value was the last available value on or prior to first dose date of any study drug. Improvement (decrease) indicated the change in MELD score (post-treatment visits minus baseline score) was less than 0.
Source: Clinical Study Reports: ASTRAL-4.[43]

TABLE 24: DECREASE, NO CHANGE, OR INCREASE IN MELD SCORE BETWEEN BASELINE AND POST-TREATMENT BY CTP SCORE, MELD SCORE, ASCITES, ENCEPHALOPATHY, ALBUMIN, AND PLATELETS

	ASTRAL-4		
	SOF/VEL + RBV for 12 weeks		
	CTP Score Between Baseline and Post-Treatment Week 12		
	Decrease (Improvement) (N = 41)	No Change (N = 12)	Increase (Worsening) (N = 28)
Baseline CTP Class			
CTP A (5 to 6)	3/ 5 (60.0)	0	2/5 (40.0)
CTP B (7 to 9)	37/72 (51.4)	12/72 (16.7)	23/72 (31.9)
CTP C (10 to 12)	1/ 4 (25.0)	0	3/ 4 (75.0)
Baseline MELD Score			
< 15	34/71 (47.9)	10/71 (14.1)	27/71 (38.0)
≥ 15	7/10 (70.0)	2/10 (20.0)	1/10 (10.0)
Baseline Ascites			
None	12/21 (57.1)	3/21 (14.3)	6/21 (28.6)
Mild/Moderate	29/56 (51.8)	8/56 (14.3)	19/56 (33.9)
Severe	0	1/ 4 (25.0)	3/ 4 (75.0)
Baseline Encephalopathy			
None	19/30 (63.3)	3/30 (10.0)	8/30 (26.7)
Grade 1 to 2	22/51 (43.1)	9/51 (17.6)	20/51 (39.2)
Baseline Albumin (g/dL)			
≤ 3	22/38 (57.9)	5/38 (13.2)	11/38 (28.9)
> 3	19/43 (44.2)	7/43 (16.3)	17/43 (39.5)
Baseline Platelets (x 10^3/µL)			
< 75	17/28 (60.7)	5/28 (17.9)	6/28 (21.4)
≥ 75	24/53 (45.3)	7/53 (13.2)	22/53 (41.5)

CTP = Child–Turcotte–Pugh; MELD = Model for End-Stage Liver Disease; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Note: Baseline value is the last available value on or prior to first dose date of any study drug. No change was assigned for differences (post-treatment visits minus baseline score) of 0; decrease will be assigned for differences that are less than 0; and increase will be assigned for values that are greater than 0.
Source: Clinical Study Reports: ASTRAL-4.[43]

TABLE 25: CTP CHANGE FROM BASELINE TO POST-TREATMENT VISITS NUMBER (%) FOR PATIENTS WHO ACHIEVED SVR12 IN ASTRAL-4

CTP Change From Baseline at Post-Treatment Week 12	ASTRAL-4	
	SOF/VEL + RBV for 12 weeks (N = 82)	
–5	0/81	Decrease (Improvement) = 33/81 (40.7)
–4	0/81	
–3	2/81 (2.5)	
–2	10/81 (12.3)	
–1	21/81 (25.9)	
0	40/81 (49.4)	No Change = 40/81 (49.4)
1	4/81 (4.9)	[redacted]

CTP Change From Baseline at Post-Treatment Week 12	ASTRAL-4	
	SOF/VEL + RBV for 12 weeks (N = 82)	
–5	0/81	Decrease (Improvement) = 33/81
2	3/81 (3.7)	
4	0/81	
5	1/81 (1.2)	
No Assessment	1	No Assessment = 1

CTP = Child–Turcotte–Pugh; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Source: Clinical Study Reports: ASTRAL-4.[43]

TABLE 26: SHIFT OF CTP CLASS AT BASELINE AND AT POST-TREATMENT VISITS FOR PATIENTS WHO ACHIEVED SVR12 IN ASTRAL-4

	ASTRAL-4			
	SOF/VEL + RBV for 12 weeks			
	Post-Treatment Week 12 CTP Class			
Baseline CTP Class	**CTP A (5 to 6)**	**CTP B (7 to 9)**	**CTP C (10 to 15)**	**No Assessment**
CTP A (5 to 6)	3/5 (60.0)	2/5 (40.0)	[redacted]	1
CTP B (7 to 9)	8/72 (11.1)	63/72 (87.5)	1/72 (1.4)	0
CTP C (10 to 12)	0/4	1/4 (25.0)	3/4 (75.0)	0

CTP = Child–Turcotte–Pugh; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Source: Clinical Study Reports: ASTRAL-4.[43]

TABLE 27: COMPONENTS OF CTP FOR PATIENTS WITH IMPROVEMENT IN CTP SCORE BETWEEN BASELINE AND POST-TREATMENT VISITS FOR PATIENTS WHO ACHIEVED SVR12 IN ASTRAL-4

	ASTRAL-4				
	SOF/VEL + RBV for 12 weeks				
	Albumin	**Bilirubin**	**INR**	**Ascites**	**Encephalopathy**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

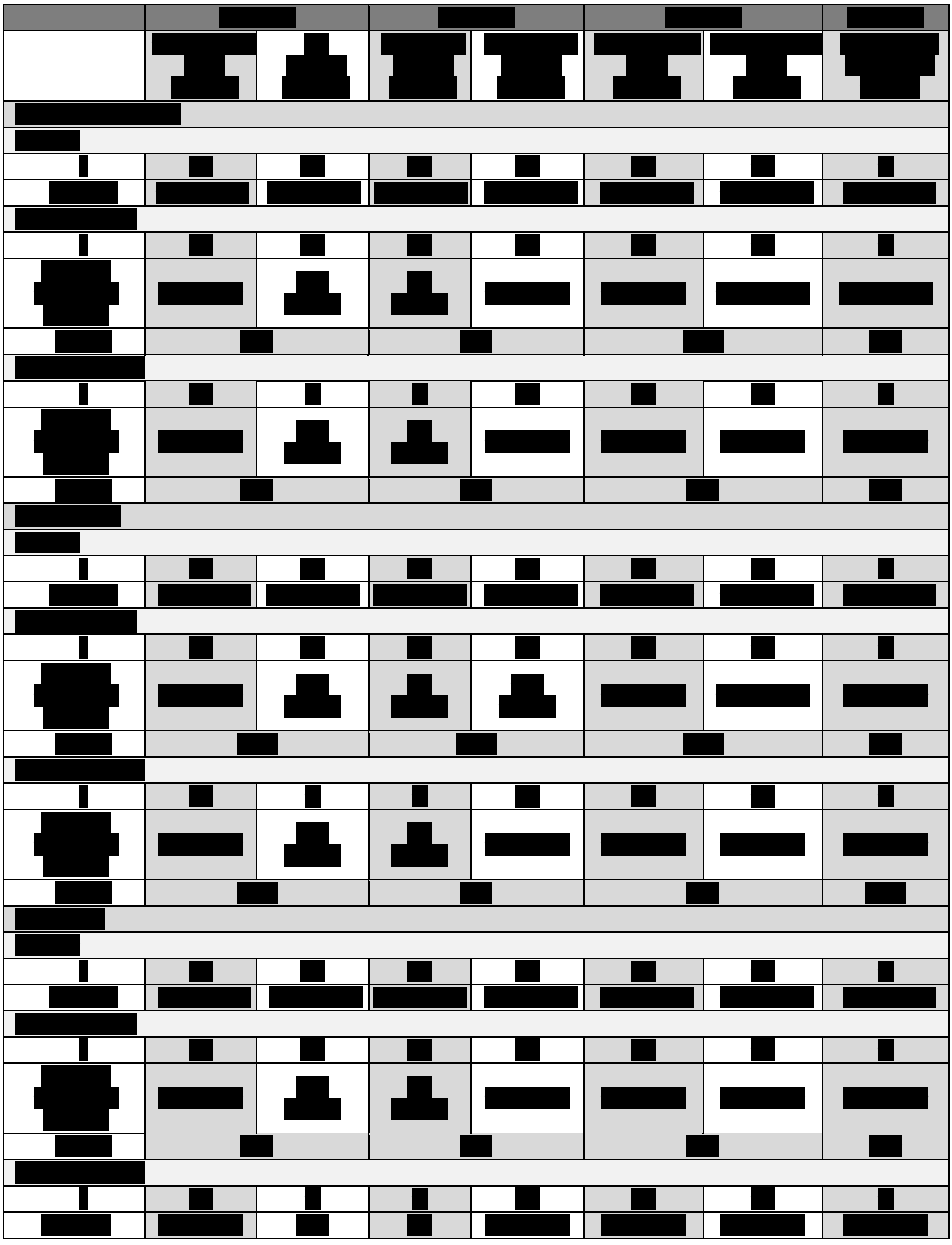
CTP = Child–Turcotte–Pugh; INR = international normalized ratio; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment; VEL = velpatasvir.
Note: Baseline value was the last available value on or prior to first dose date of any study drug. Improvement (decrease) indicated the change in CTP score (post-treatment visits minus baseline score) was less than 0.
Source: Clinical Study Reports: ASTRAL-4.[43]

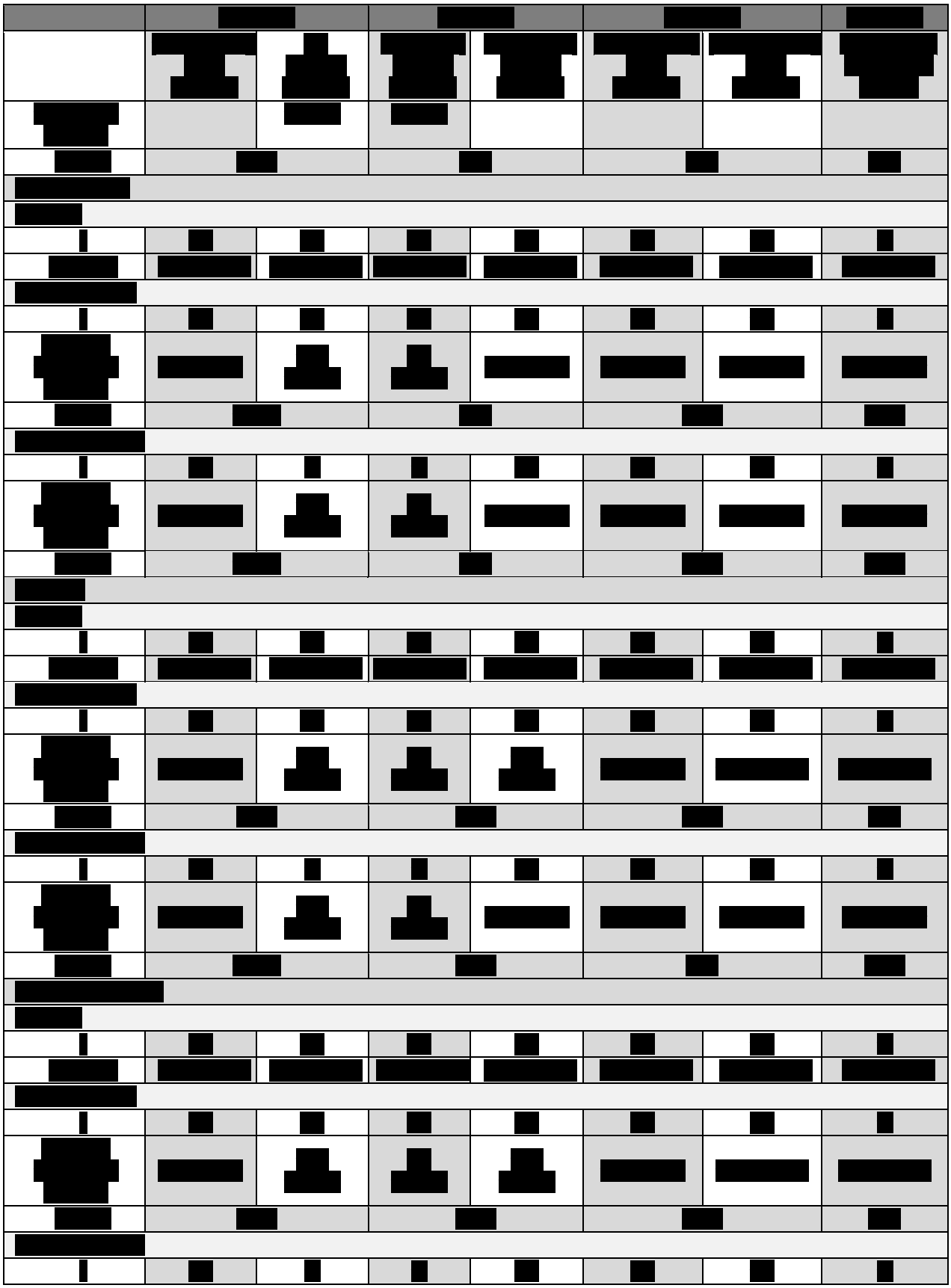
TABLE 28: DECREASE, NO CHANGE, OR INCREASE IN CTP SCORE BETWEEN BASELINE AND POST-TREATMENT BY CTP SCORE, MELD SCORE, ASCITES, ENCEPHALOPATHY, ALBUMIN, AND PLATELETS

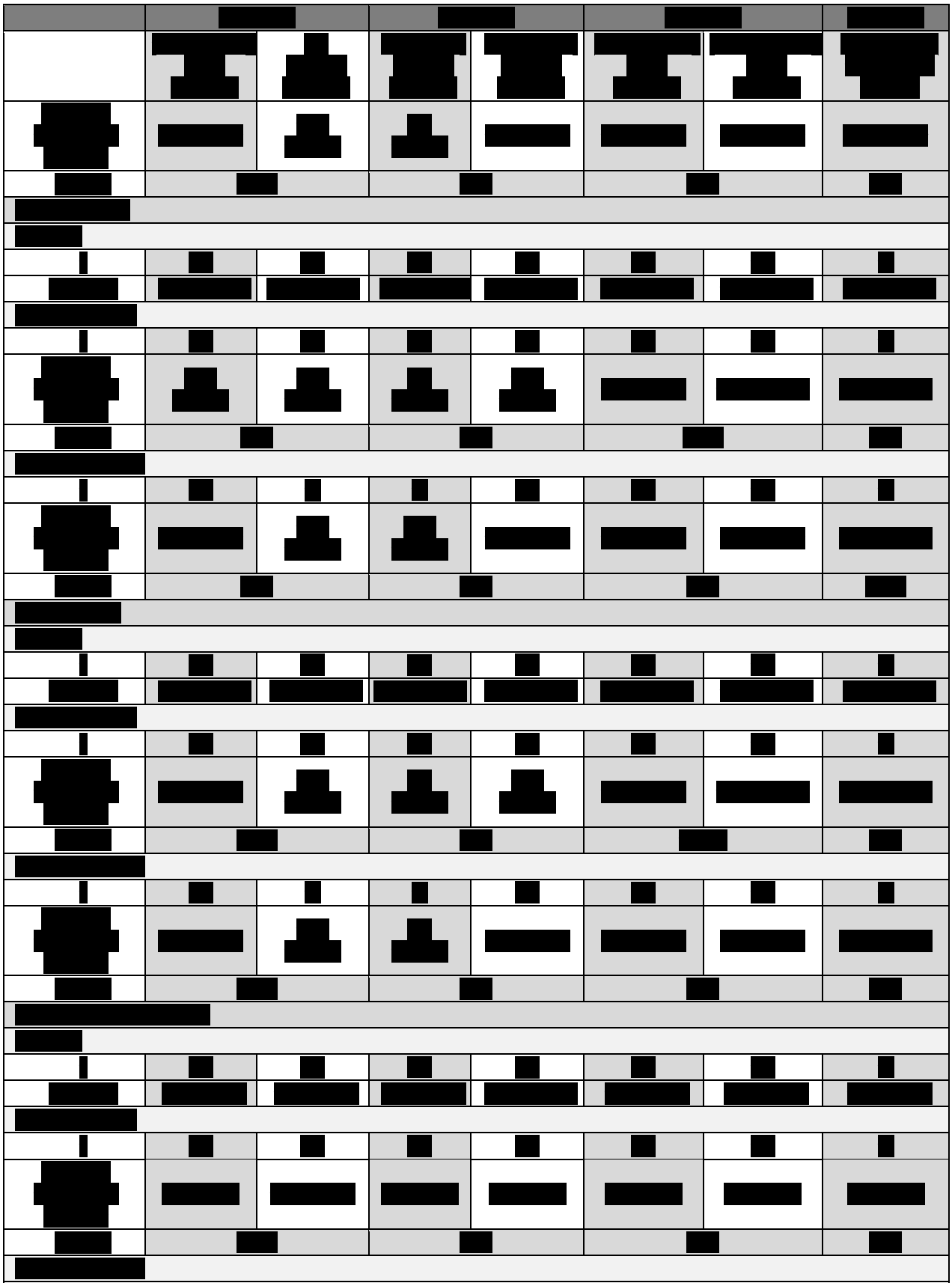
	ASTRAL-4		
	SOF/VEL + RBV for 12 weeks		
	CTP Score Between Baseline and Post-Treatment Week 12		
	Decrease (Improvement) (N = 33)	No Change (N = 40)	Increase (Worsening) (N = 8)
Baseline CTP Class			
CTP A (5 to 6)	1/5 (20.0)	2/5 (40.0)	2/5 (40.0)
CTP B (7 to 9)	31/72 (43.1)	36/72 (50.0)	5/72 (6.9)
CTP C (10 to 12)	1/4 (25.0)	2/4 (50.0)	1/4 (25.0)
Baseline MELD Score			
< 15	27/71 (38.0)	37/71 (52.1)	7/71 (9.9)
≥ 15	6/10 (60.0)	3/10 (30.0)	1/10 (10.0)
Baseline Ascites			
None	8/21 (38.1)	8/21 (38.1)	5/21 (23.8)
Mild/Moderate	24/56 (42.9)	29/56 (51.8)	3/56 (5.4)
Severe	1/4 (25.0)	3/ 4 (75.0)	0
Baseline Encephalopathy			
None	12/30 (40.0)	15/30 (50.0)	3/30 (10.0)
Grade 1 to 2	21/51 (41.2)	25/51 (49.0)	5/51 (9.8)
Baseline Albumin (g/dL)			
≤ 3	14/38 (36.8)	18/38 (47.4)	6/38 (15.8)
> 3	19/43 (44.2)	22/43 (51.2)	2/43 (4.7)
Baseline Platelets (x 10^3/µL)			
< 75	19/28 (67.9)	8/28 (28.6)	1/28 (3.6)
≥ 75	14/53 (26.4)	32/53 (60.4)	7/53 (13.2)

CTP = Child–Turcotte–Pugh; MELD = Model for End-Stage Liver Disease; SOF = sofosbuvir; VEL = velpatasvir.
Note: Baseline value was the last available value on or prior to first dose date of any study drug. No change was assigned for differences (post-treatment visit minus baseline score) of 0; decrease was assigned for differences that were less than 0; and increase was assigned for values that were greater than 0.
Source: Clinical Study Reports: ASTRAL-4.[43]

TABLE 29: SUMMARY OF SF-36 QUALITY OF LIFE QUESTIONNAIRE





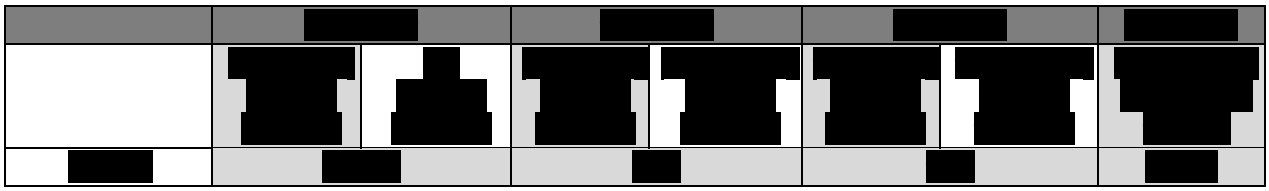


[redacted]

SF-36 = Short Form (36) Health Survey; SOF = sofosbuvir; VEL = velpatasvir.
[a] *P* value reported is for between-treatment difference.
[b] *P* value reported is for within-group difference.
Source: Clinical Study Reports: ASTRAL-1,[40] ASTRAL-2,[41] ASTRAL-3,[42] ASTRAL-4.[43]

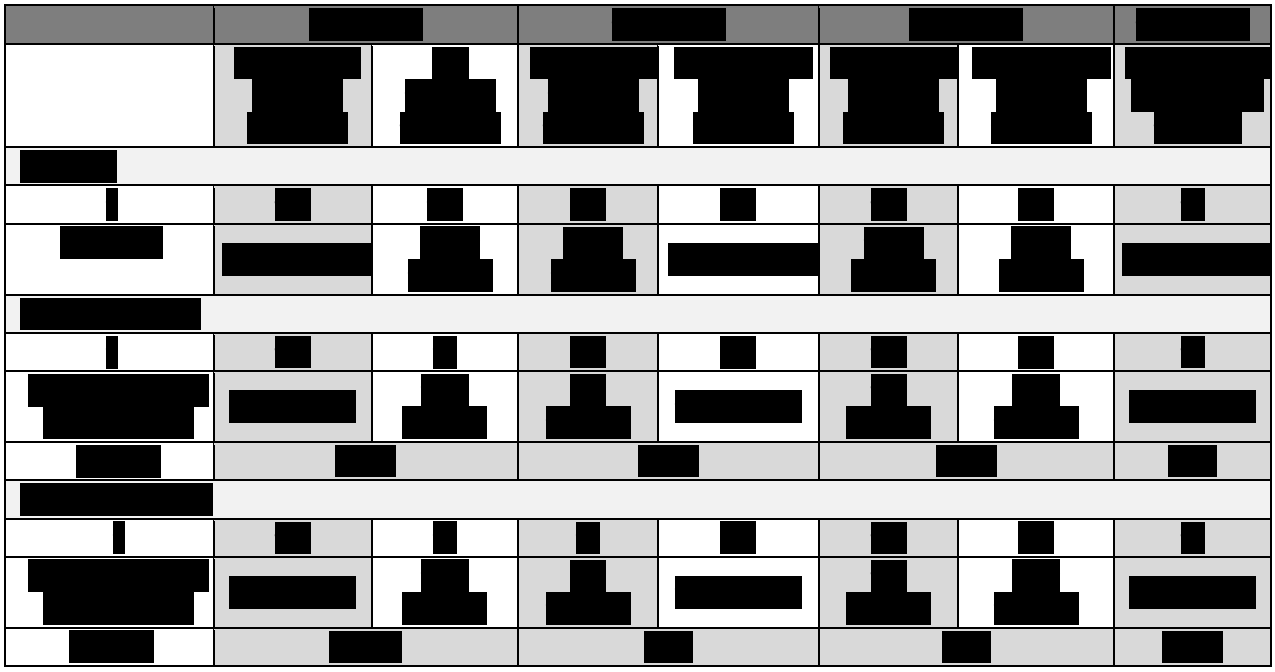
TABLE 30: SUMMARY OF OVERALL CLDQ-HCV SCORE

[redacted]



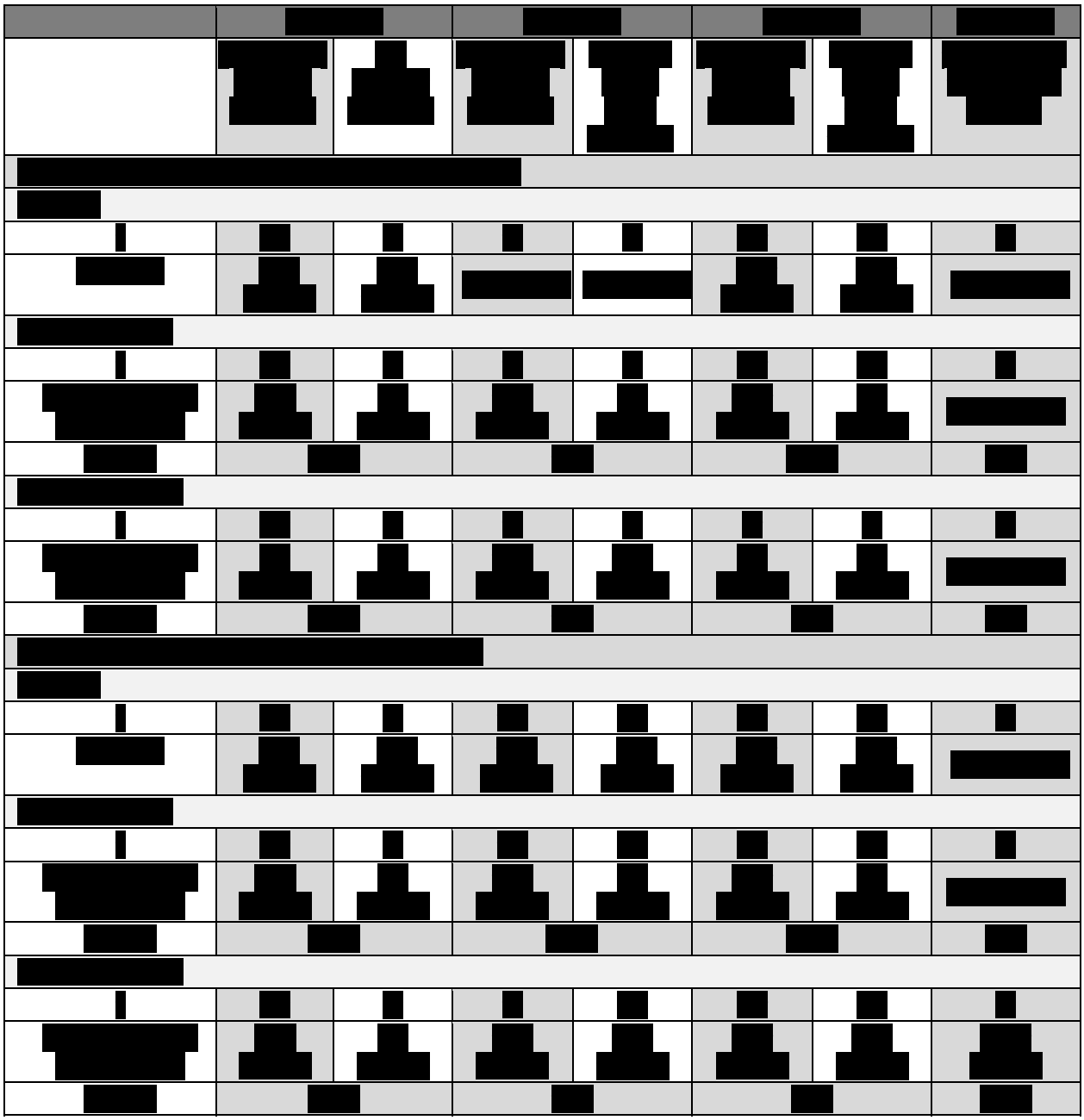
CLDQ-HCV = Chronic Liver Disease Questionnaire–Hepatitis C; SOF = sofosbuvir; VEL = velpatasvir.
[a] *P* value reported is for between-treatment difference.
[b] *P* value reported is for within-group difference.
Source: Clinical Study Reports: ASTRAL-1,[40] ASTRAL-2,[41] ASTRAL-3,[42] ASTRAL-4.[43]

TABLE 31: SUMMARY OF FACIT-F TOTAL SCORE



FACIT-F = Functional Assessment of Chronic Illness–Fatigue; SOF = sofosbuvir; VEL = velpatasvir.
[a] *P* value reported is for between-treatment difference.
[b] *P* value reported is for within-group difference.
Source: Clinical Study Reports: ASTRAL-1,[40] ASTRAL-2,[41] ASTRAL-3,[42] ASTRAL-4.[43]

TABLE 32: SUMMARY OF OVERALL WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT–HEPATITIS C SCORE



SOF = sofosbuvir; VEL = velpatasvir; WPAI-Hep C = Work Productivity and Activity Impairment–Hepatitis C.
[a] *P* value reported is for between-treatment difference.
[b] *P* value reported is for within-group difference.
Source: Clinical Study Reports: ASTRAL-1,[40] ASTRAL-2,[41] ASTRAL-3,[42] ASTRAL-4.[43]

TABLE 33: ADVERSE EVENTS FOR AT LEAST 5% OF PATIENTS

	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 weeks (n = 624)	PBO 12 weeks (n = 116)	SOF/VEL for 12 weeks (n = 134)	SOF + RBV for 12 weeks (n = 132)	SOF/VEL for 12 weeks (n = 277)	SOF + RBV for 24 weeks (n = 275)	SOF/VEL + RBV for 12 weeks (n = 87)
Headache	[redacted]	33 (28.4)	[redacted]	29 (22.0)	[redacted]	89 (32.4)	18 (20.7)
Fatigue	[redacted]	23 (19.8)	[redacted]	47 (35.6)	[redacted]	105 (38.2)	34 (39.1)
Nasopharyngitis	[redacted]	12 (10.3)	[redacted]	2 (1.5)	[redacted]	33 (12.0)	
Nausea	[redacted]	13 (11.2)	[redacted]	19 (14.4)	[redacted]	58 (21.1)	22 (25.3)
Insomnia	[redacted]	11 (9.5)	[redacted]	18 (13.6)	[redacted]	74 (26.9)	12 (13.8)
Diarrhea	[redacted]	8 (6.9)			[redacted]	21 (7.6)	18 (20.7)
Asthenia	[redacted]	9 (7.8)			[redacted]	26 (9.5)	
Arthralgia	[redacted]	9 (7.8)	[redacted]	8 (6.1)	[redacted]	22 (8.0)	
Cough	[redacted]	4 (3.4)			[redacted]	35 (12.7)	9 (10.3)
Back pain	[redacted]	11 (9.5)	[redacted]	7 (5.3)	[redacted]	20 (7.3)	
Myalgia	[redacted]	6 (5.2)			[redacted]	[redacted]	
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	
Irritability			[redacted]	9 (6.8)	[redacted]	40 (14.5)	
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	
Upper respiratory tract infection			[redacted]	5 (3.8)			
Vomiting			[redacted]	[redacted]	[redacted]	[redacted]	5 (5.7)
Abdominal pain			[redacted]	[redacted]	[redacted]	[redacted]	6 (6.9)
[redacted]			[redacted]	[redacted]			
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	
Rash			[redacted]	[redacted]	[redacted]	[redacted]	5 (5.7)
Anemia			[redacted]	[redacted]	[redacted]	[redacted]	27 (31.0)
[redacted]					[redacted]	[redacted]	
[redacted]					[redacted]	[redacted]	
Dyspnea					[redacted]	[redacted]	9 (10.3)
Muscle spasms					[redacted]	[redacted]	10 (11.5)
[redacted]					[redacted]	[redacted]	
[redacted]					[redacted]	[redacted]	
[redacted]					[redacted]	[redacted]	
[redacted]					[redacted]	[redacted]	
[redacted]					[redacted]	[redacted]	
[redacted]					[redacted]	[redacted]	
Ascites							5 (5.7)
Abdominal discomfort							5 (5.7)

	ASTRAL-1		ASTRAL-2		ASTRAL-3		ASTRAL-4
	SOF/VEL for 12 weeks (n = 624)	PBO 12 weeks (n = 116)	SOF/VEL for 12 weeks (n = 134)	SOF + RBV for 12 weeks (n = 132)	SOF/VEL for 12 weeks (n = 277)	SOF + RBV for 24 weeks (n = 275)	SOF/VEL + RBV for 12 weeks (n = 87)
Edema, peripheral							6 (6.9)
Hepatic encephalopathy							5 (5.7)
Hypertension							5 (5.7)

PBO = placebo; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir.
Source: Clinical Study Reports: ASTRAL-1,[40] ASTRAL-2,[41] ASTRAL-3,[42] ASTRAL-4.[43]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Sustained virologic response at 12 weeks (SVR12) as a surrogate for SVR at 24 weeks (SVR24)
- Short Form 36-item instrument (SF-36)
- Chronic Liver Disease Questionnaire–Hepatitis C (CLDQ-HCV)
- Functional Assessment of Chronic Illness–Fatigue (FACIT-F)
- Work Productivity and Activity Impairment–Hepatitis C (WPAI-Hep C)
- Child–Turcotte–Pugh (CTP)
- Model for End-Stage Liver Disease (MELD).

Findings

The above-mentioned outcome measures are briefly summarized in Table 34.

TABLE 34: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID	References
SVR12 and 24	SVR at weeks 12 and 24 are end points for assessing response to agents that treat CHC infection.	Yes	Not applicable	Chen et al.[63]
SF-36	SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL.	Yes	2 to 4	Ware et al.[52]
CLDQ-HCV	The CLDQ is an HRQoL instrument for patients with chronic liver disease.	Yes	0.5	Younossi et al.[44]
FACIT-F	FACIT-F is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, and lack of energy, as well as fatigue's impact on daily activities and function.	No	Unknown	CSR[45]
WPAI-Hep C	WPAI is an instrument used to measure the impact of a disease on work and on daily activities.	No	Unknown	Reilly et al.[64]
CTP	The CTP is a scoring instrument used to categorize the severity of patients with cirrhosis according to criteria in 5 categories. It was previously used as a criterion for prioritizing liver transplant candidates.	Yes	Not applicable	Child et al.[65] Pugh et al.[54]
MELD	The MELD score is calculated based on 4 objective prognostic values and used to assess the risk of mortality in patients with cirrhosis. It is currently	Yes	Not applicable	Malinchoc et al.[55]

Instrument	Type	Evidence of Validity	MCID	References
	used as a criterion for prioritizing liver transplant candidates.			

CHC = chronic hepatitis C; CLDQ-HCV = Chronic Liver Disease Questionnaire–Hepatitis C; CSR = Clinical Study Report; CTP = Child–Turcotte–Pugh; FACIT-F= Functional Assessment of Chronic Illness–Fatigue; HRQoL = health-related quality of life; MCID = minimal clinically important difference; MELD = Model for End-Stage Liver Disease; SF-36= Short Form (36) Health Survey; SVR12 and 24 = sustained virologic response at 12 weeks (SVR12) as a surrogate for SVR at 24 weeks (SVR24); WPAI-Hep C = Work Productivity and Activity Impairment–Hepatitis C.

SVR12 and 24

SVR24 is the standard primary end point for assessing response to drugs that treat chronic hepatitis C (CHC) infection.[63] However, SVR12 is an emerging outcome of interest, potentially providing a means for determining treatment response earlier in either randomized controlled trials or the clinic. In 2013, the FDA published a paper that sought to determine the predictive value of SVR12 as a surrogate for SVR24.[63] The authors reviewed data submitted to the FDA (2002-2011) from 15 phase 2 and 3 studies that included various treatment durations of pegylated interferon alfa-2a, pegylated interferon alfa-2b, albinterferon alfa-2b, telaprevir, and boceprevir. The majority of the 13,599 participants had genotype 1 infection (N = 11,730), while 69 patients had genotype 4. In addition to assessing SVR12, the authors also reviewed the predictive value of SVR4 with respect to SVR24.

SVR12 was achieved by 51.8% (7,051 of 13,599 patients) and SVR24 by 50.6% (6,881 of 13,599 patients) of adults in the database.[63] The positive predictive value between SVR12 and SVR24 was 98.3% and the negative predictive value was 98.8%. Thus, 1.2% of patients would be falsely identified as not achieving SVR if an outcome of SVR12 was adopted over SVR24, and 1.7% of patients would be falsely identified as having a sustained undetectable viral load. The authors attributed the latter to relapse, reinfection, or "other" reasons. Results were consistent across the 15 studies, with between 0% and 4.3% of patients achieving SVR12 but not SVR24. Older studies that used hepatitis C virus (HCV) ribonucleic acid (RNA) assays with higher values for lower limits of detection had lower positive predictive values than those studies with newer, more sensitive assays. Overall, the authors concluded that SVR12 would be an appropriate primary end point for trials used by regulatory bodies to evaluate CHC treatments.[63] They also stated that these conclusions should be applied with caution to direct-acting antiviral (DAA)–only regimens, considering that they were based on data from regimens containing interferon plus ribavirin.[63] Further monitoring of interferon-free clinical trials may be required to determine the appropriate end point.

A study published in 2010 also evaluated the relevance of SVR12 as a primary outcome.[66] This study included 781 patients with CHC; all had received pegylated interferon plus ribavirin (PR). Among the 781 individuals, 74 patients had genotype 4 or 5 CHC (genotype 4 was not reported separately from genotype 5). Of the 781 patients, 573 had an end-of-treatment response and were thus included in the analysis. Of the 409 patients who had an SVR12, 408 went on to have an SVR24.[66] Therefore, this study also demonstrated a high concordance between achievement of SVR12 and eventual achievement of SVR24. The authors concluded that SVR12 is as informative as SVR24 when assessing SVR. This study used the transcription-mediated amplification assay, which is a newer, more sensitive assay.

Another study explored differences between SVR12 and SVR24 among treatment-naive genotype 1 CHC patients who received PR.[67] The authors pooled single-arm data for pegylated interferon alfa-2a or alfa-2b plus ribavirin from 35 clinical trials. Of these trials, only one study reported both SVR12 and SVR24.

The proportion with an SVR12 or SVR24 was pooled across trials using a DerSimonian-Laird random-effects model. Data for SVR12, SVR24, and for each type of pegylated interferon were pooled separately. The authors also performed a Bayesian random-effects meta-regression of the proportion with SVR12 or SVR24, controlling for the type of pegylated interferon. The authors concluded that SVR12 was 5% to 6% higher than SVR24, although the credible intervals (CrIs) overlapped in the conventional meta-analysis, and in the Bayesian meta-regression, the CrIs included the null value (SVR12 versus SVR24 relative risk 1.13; 95% CrI, 0.99 to 1.26).[67] These findings should be interpreted with caution, considering that they were based on single treatment group data. Naive pooling of single-arm data is not an acceptable method for determining comparative efficacy, as it ignores the benefits of randomization and may therefore be subject to the same biases as a comparison of independent cohort studies. In addition, the analysis was limited to data from patients who received PR, and did not examine the concordance of SVR12 and SVR24 among those who received a DAA regimen.

One study performed an analysis of the concordance between SVR12 and SVR24 using pooled data from phase 3 clinical trials of sofosbuvir-containing regimens (NEUTRINO, FISSION, POSITRON, FUSION, and VALENCE).[68] From this analysis, a total of 777 of 779 patients (99.7%) who achieved SVR12 also achieved SVR24, including all patients (n = 296) with hepatocellular carcinoma (HCC) genotype 1 or 4 to 6, all patients (n = 270) with genotype 2, and 211 or 213 patients (99.0%) with genotype 3. Thus, the negative predictive value measuring concordance between SVR12 and SVR24 was 100% and positive predictive value was 99.7%.

Short Form 36-Item health survey

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on 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 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.[52]

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

- A total of 15 studies with SF-36 were included that compared HRQoL in patients with compensated hepatitis C seropositivity versus healthy controls. All 15 studies provided cross-sectional group mean HRQoL differences stratified by hepatitis C status (the clinical anchor). Patients with hepatitis C scored lower on the various domains compared with healthy patients. The largest impact of the disease was on role physical, role emotional, and general health (Table 35).[51]
- A panel of experts was convened to indirectly estimate the minimal clinically important difference (MCID) in hepatitis C based upon existing HRQoL data.[51] The panel consisted of three hepatologists and two HRQoL methodologists with expertise in chronic liver disease–specific HRQoL. Based on the results of the systematic review, the panel determined that the SF-36 vitality scale captures the HRQoL domain that is most relevant to patients with hepatitis C. Using a modified Delphi

technique, the expert panel generated a mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale, with a corresponding effect size of 0.2 (range 0.15 to 0.25).[51] MCIDs for other dimensions or for the two component scores were not estimated. Of note, this study did not use an anchor-based method, which may be preferred, to generate the MCID and, as such, it is unclear if the estimates represent values patients would identify as clinically important.[69]

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

TABLE 35: HEPATITIS C PATIENTS VERSUS HEALTHY CONTROLS 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

Chronic Liver Disease Questionnaire–Hepatitis C

The CLDQ is an HRQoL instrument for patients with chronic liver disease. CLDQ includes 29 items, divided into six domains: Abdominal Symptoms, Fatigue, Systemic Symptoms, Activity, Emotional Function, and Worry. For each item, the patient assigns a score of 1 (all the time) to 7 (none of the time). The domain score is the sum of the item scores for that domain, divided by the number of items in that respective domain. The overall CLDQ score is the mean of the domain scores. Scores are presented on a 1 to 7 scale, with higher numbers indicating the best possible function.[44] In the paper by Younossi et al.,[44] the investigators stated that a change of 0.5 on the 1 to 7 scale would signify an important difference in questionnaire score; however, there is no proof of validation of this MCID.[69]

It appears that the CLDQ was subsequently amended for use in CHC patients. From abstracts, we could find that scores are based on a Likert scale from 0 (worst) to 7 (best) and measure Activity/Energy, Emotion, Worry, Systemic, and CLDQ-HCV Total score.[70,71] No detailed information was available.

An MCID for CLDQ-HCV has not been estimated, although one abstract[71] cited an MCID of 0.5, perhaps in reference to the paper by Younossi et al.[44] mentioned above.

Three abstracts on convergent validity and one abstract on construct validity of CLDQ-HCV were identified.[70-73]

Convergent validity

CLDQ-HCV was validated against the Fatigue Severity Scale (high score = more fatigue) in 100 consecutive healthy blood donors and from 50 CHC patients.[72] Correlations between Fatigue Severity Scale and CLDQ-HCV in the 100 healthy blood donors were as follows: Activity/ Energy, r = –0.65 (*P* = 0.0001); Emotion, r = –0.61 (*P* < 0.0001); Worry, r = –0.23 (*P* < 0.0001); Systemic, r = –0.39, (*P* < 0.0001); and Overall Score, r = 0.58 (*P* < 0.0001). Comparison of CLDQ-HCV scores between blood donor patients and CHC patients showed statistically significant differences in HRQoL measured by Worry (*P* < 0.0001), Emotion (*P* = 0.048), and Overall Score (*P* = 0.004), with worse (lower) scores in CHC patients.[72]

CLDQ-HCV was validated against SF-36 in 50 hepatitis C patients. CLDQ-HCV Activity/Energy (A/E) domain and SF-36 vitality (VT) and physical functioning (PF) scales were used. Statistically significant correlations were shown (VT versus A/E, r = 0.84 [*P* < 0.0001]; VT versus PF, r = 0.48 [*P* < 0.0001]).[73] In another abstract, CLDQ-HCV was validated against SF-36 in 63 hepatitis C patients. The r values obtained are shown in Table 36.[70] All findings were statistically significant.

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

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

CLDQ-HCV = Chronic Liver Disease Questionnaire–Hepatitis C Virus; NR = not reported; SF-36 = Short Form (36) Health Survey.
Source: Escheik et al.[70]

Construct validity

One abstract presented data on the validation of CLDQ-HCV in 62 hepatitis C patients versus 100 healthy blood donors.[71] Hepatitis C patients received PR treatment. Hepatitis C patients had lower (worse) CLDQ-HCV Overall Score at baseline compared with healthy controls (5.7 ± 0.7 versus 6.2 ± 0.5, *P* < 0.0001). Lower scores were also reported at baseline for Emotion and Worry in hepatitis C patients (5.6 ± 0.4 and 5.7 ± 0.9) compared with healthy controls (5.9 ± 0.4 and 6.9 ± 0.2), respectively. After 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.[71]

Functional Assessment of Chronic Illness Therapy–Fatigue

The Functional Assessment of Cancer Therapy (FACT) was originally developed and validated in cancer patients.[74] The Functional Assessment of Chronic Illness Therapy (FACIT) was later derived from FACT and validated in patients with chronic conditions such as multiple sclerosis and rheumatoid arthritis.[47] The FACIT measurement system is based on a generic core questionnaire (FACT–General) that includes 27 items divided into four primary domains: physical, social/family, emotional, and functional well-being.[47] The FACIT-F is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, and lack of energy, as well as fatigue's impact on daily activities and function, and includes an additional 13 items scored using a 5-point Likert-type response scale to rate each item, where 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much, with a recall period of "during the past 7 days".[45] 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).[46] Although no information on the validity of FACIT-F or its MCID in hepatitis C patients was found, the MCID for the FACT–General total score ranged from 3 to 7 points in cancer patients, and the MCID in the FACIT-F ranged from 3 to 4 points in rheumatoid arthritis patients.[47,48]

Work Productivity and Activity Impairment–Hepatitis C

The WPAI questionnaire is an instrument used to measure the impact of a disease on work and on 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 [VAS]); Q6 = degree health affected productivity in regular unpaid activities (VAS).[49,50,64] 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 (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 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; 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 will 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.[49,50]

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.[75]

Although no information on the validity of 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 disease.[50]

Child–Turcotte–Pugh

The CTP classification was originally developed in 1964 to evaluate the risk of surgical portosystemic shunt procedures, and was subsequently found to predict long-term survival in patients with cirrhosis.[53,54] A CTP score is calculated based on clinical and lab criteria, with points ranging from 1 to 3 assigned to specific criteria within five categories: hepatic encephalopathy, ascites, total bilirubin, serum albumin, and international normalized ratio (INR) (Table 37). Points from each criterion are added to determine the CTP score and class: Class A, 5 to 6 points; class B, 7 to 9 points; class C, 10 to 15 points. The CTP classification can differentiate between patients with poor liver function and preserved liver function, and higher scores indicate worsening liver function.

TABLE 37: CHILD–TURCOTTE–PUGH CRITERIA

Criteria	Points
Hepatic encephalopathy	
None	+1
Mild to moderate (grade 1 or 2, or suppressed with medication)	+2
Severe (grade 3 or 4, or refractory)	+3
Ascites	
None	+1
Mild to moderate (diuretic responsive)	+2
Severe (diuretic refractory)	+3
Total bilirubin (µmol/L)	
< 34	+1
34 to 50	+2
> 50	+3
Serum albumin (g/L)	
> 35	+1
28 to 35	+2
< 28	+3
International normalized ratio	
< 1.7	+1
1.7 to 2.3	+2
> 2.3	+3

The CTP has commonly been used in preoperative risk stratification in cirrhotic patients undergoing surgery. In a 1984 retrospective review of 100 consecutive patients (30 women, 70 men) with liver cirrhosis who underwent celiotomy at a single centre in the US, the mortality rates for patients undergoing surgery were 10% for patients with Child's class A, 31% for patients with Child's class B, and 76% for patients with Child's class C.[76] Similar results were seen in a 1997 retrospective study of 92 patients with cirrhosis that required abdominal operations over a 12-year period, where the mortality rates for patients undergoing surgery were 10% for patients with Child's class A, 30% for patients with Child's class B, and 82% for patients with Child's class C.[77]

The CTP, along with blood type compatibility and overall wait time, was used to allocate liver donations to potential liver recipients among patients with chronic liver disease prior to 2002 in the US, according to the United Network for Organ Sharing (UNOS). Patients with acute liver failure would receive priority for liver allocation (Status 1), but patients with chronic liver disease were ranked using the criteria listed in Table 38.[56] As there were only three categories for patients with cirrhosis, the time spent on the waiting list became the major determinant of who would receive a liver transplant rather than the risk of mortality.[78]

TABLE 38: UNITED NETWORK FOR ORGAN SHARING STATUS CRITERIA FOR PATIENTS WITH CHRONIC LIVER DISEASE PRIOR TO 2002

Status	Criteria
Status 2A	CTP score ≥ 10, ICU care, and estimated to have < 7 days to live
Status 2B	CTP score ≥ 10 or ≥ 7 associated with refractory complications of portal hypertension or hepatocellular cancer meeting the following criteria: 1 lesion < 5 cm or ≤ 3 lesions all < 3 cm each and no evidence of metastatic disease
Status 3	CTP ≥ 7 minimal listing

CTP = Child–Turcotte–Pugh; ICU = intensive care unit.
Source: Wiesner et al., 2003.[56]

Limitations of the CTP include the lack of ability to discriminate among the majority of patients undergoing portosystemic shunt procedures who may fall in class C (more severe patients). In addition, the ascites and hepatic encephalopathy categories are based on subjective assessments, making the CTP difficult to accurately reproduce.[55] Due to limitations with the CTP, the MELD was developed in 2000 in order to have a more objective measurement that could accurately predict mortality risk.[55]

Model for End-Stage Liver Disease

The MELD was developed in 2000 using 231 consecutive patients with cirrhosis who underwent an elective transjugular intrahepatic portosystemic shunt (TIPS) procedure at one of four centres in the US and who were followed up for mortality and liver transplantation outcomes, and the model was then validated using an independent set of 71 patients who underwent TIPS in the Netherlands.[55] Cox proportional hazards regression was used to identify variables that predicted survival. From this analysis, creatinine, bilirubin, INR, and the cause of cirrhosis were identified as independent predictors of survival after TIPS.[55] The MELD score is calculated by combining these four prognostic values with their corresponding regression coefficients in the following equation: **$0.957 \times \log_e$(creatinine mg/dL) + $\log_e$(bilirubin mg/dL) + $1.120 \times \log_e$(INR) + 0.643 x (cause of cirrhosis)**. For cause of cirrhosis, a value of 0 was assigned to alcohol-related or cholestatic liver disease, while a value of 1 was assigned to all other causes. In subsequent studies, the cause of cirrhosis was determined to be a less important variable in predicting survival and was removed.[78] Scores range from 6 to 40, with higher scores indicating more severe disease.

The MELD has been the method used for organ allocation for liver transplantation in the United States since 2002, where patients are ranked according to severity of liver disease and mortality risk.[56] With the introduction of MELD, the accrual of waiting time was no longer necessary for a patient to move up the wait list.[78] The current UNOS criteria used to allocate livers to patients with chronic liver disease includes the donor's age, the medical urgency of the patient, and the patient's geographical proximity to the donor.[57] Local and regional patients with sudden and severe onset liver failure (Status 1A) or very sick, chronically ill pediatric patients (Status 1B) will get first allocation of livers.[57] For patients 12 years

or older who fall outside these categories, livers are allocated according to the following ranking (patients younger than 12 years use a slightly modified scoring system called the Pediatric End-Stage Liver Disease Model [PELD]), with local candidates prioritized before regional and national candidates in the same score range:[57]

- Candidates with MELD score ≥ 35 (local, then regional)
- Candidates with MELD score ≥ 15 (local, then regional)
- Status 1a or 1b national candidates
- National candidates with MELD score ≥ 15
- Candidates with MELD score < 15 (local, regional, then national).

The implementation of MELD led to a 12% reduction in liver transplant waiting list registrations in 2002, and a 15% reduction in mortality of patients on the wait list.[78]
Comparisons of the MELD with the CTP as prognostic tools in patients with cirrhosis have yielded mixed results. A retrospective study on 506 Chinese patients admitted at a single institution with chronic hepatitis B–related liver complications found that both the MELD and CTP scores could predict mortality at three months and one year.[79] At three months, the area under the curve (AUC) for the MELD and CTP scores were 0.65 and 0.75, respectively.[79] At one year, the AUC for the MELD and CTP scores were 0.63 and 0.77, respectively.[79] The differences between the MELD and CTP scores were statistically significant.[79] However, when patients who were on lamivudine therapy were excluded, the AUC for both the MELD score and CTP score were comparable (0.77 versus 0.80).[79]

Updated and integrated versions of the MELD have been developed, which has included incorporating serum sodium concentration into the MELD (MELDNa), using a MELD:sodium ratio (MESO), and integrating age and hepatic encephalopathy scores with the MELD (iMELD).[53,80-82] The MELDNa was found to be superior to the conventional MELD for predicting post-operative three-month mortality in a retrospective study of 99 patients with cirrhosis who underwent surgery and in predicting death or transplant after TIPS in 148 consecutive patients undergoing non-emergent TIPS for refractory ascites or recurrent variceal bleeding.[53] The iMELD was found to have better predictive value of three-month mortality than the conventional MELD in a retrospective study of 432 Chinese hepatitis B virus (HBV)-related cirrhotic patients who developed acute-on-chronic liver failure.[81] The MESO index was found to perform better than the MELD in predicting one-month and three-month mortality in 256 patients with cirrhosis.[82] Because of the retrospective nature of these studies and the use of different patient populations, it is difficult to make definitive conclusions regarding the comparative predictive capabilities of these models.

Limitations of the MELD include the lack of inclusion of other complications that often accompany cirrhotic patients, such as esophageal varices and hepatic encephalopathy. Although the inclusion of subjective categories was a criticism of the CTP, it appears that when assessed with consistency and uniform definitions, these categories are valuable when assessing the severity of a patient with cirrhosis. A study that looked at 290 cirrhotic patients found that there was no significant difference in MELD scores between patients with cirrhosis-related complications (n = 67) and patients without cirrhosis-related complications (n = 227).[83] In addition, despite the objectivity of the variables included in the MELD, the results of these measurements may be subject to variability due to differences in laboratory methods.[78]

Conclusion

- A review using individual patient data from 15 phase 2 and 3 studies (N = 13,599 participants), in which the majority were patients with genotype 1 (N = 11,730), suggests that SVR12 is a reliable surrogate for SVR24. The authors suggest that SVR12 may become a new definition for SVR for regulatory approval.
- SF-36, a generic health assessment questionnaire, has shown good construct validity in hepatitis C patients. A mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale has been reported. MCIDs for other dimensions or for the two component scores of the SF-36 for patients with CHC infection were not found in the literature, but the generally recommended MCID from the instrument developer for the PCS and MCS is 2 to 3 points.
- The CLDQ-HCV has shown good convergent and construct validities in hepatitis C patients. No information could be identified on the MCID of this instrument in hepatitis C, although one abstract cited an MCID of 0.5, perhaps in reference to the CLDQ-HCV.
- Although no information was found on the validity and MCID of FACIT-F in hepatitis C, the MCID in the FACIT-F ranged from 3 to 4 points in rheumatoid arthritis patients.
- 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 disease.
- The CTP and MELD are prognostic tools to classify patients with cirrhosis according to severity of disease. Both the CTP and MELD have been used to rank liver transplant candidates, with the MELD replacing the CTP in 2002 as a more objective measure that was able to assess the risk of mortality.

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