Common Drug Review
Clinical Review Report

July 2016

Drug	Asunaprevir (Sunvepra)
Indication	In combination with other agents for the treatment of chronic hepatitis C (CHC) in adult patients with hepatitis C virus (HCV) genotypes 1 or 4 and compensated liver disease, including cirrhosis.
Listing request	In combination with other agents for the treatment of chronic HCV infection and compensated liver disease (including cirrhosis) for the following regimen: • Daclatasvir + Asunaprevir: Treatment of G1b chronic HCV infection • Daclatasvir + Asunaprevir QUAD THERAPY (with pegylated interferon plus ribavarin [PR]): In a similar manner as interferon-based therapies already listed for the treatment of G1 and G4.
Dosage form(s)	100 mg capsule
NOC date	March 9, 2016
Manufacturer	Bristol-Myers Squibb

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
ASV	asunaprevir
BOC	boceprevir
CHC	chronic hepatitis C
CI	confidence interval
DAA	direct-acting antiviral
DB	double-blind
DCV	daclatasvir
DCV + ASV	daclatasvir plus asunaprevir
DCV/ASV + PR	daclatasvir plus asunaprevir and pegylated interferon plus ribavirin
EQ-5D	EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire
FDA	Food and Drug Administration
HCV	hepatitis C virus
HRQoL	health-related quality of life
IFN	interferon
ITC	indirect treatment comparison
LLOQ	lower limit of quantification
MAIC	matching-adjusted indirect comparisons
mITT	modified intention-to-treat population
NMA	network meta-analysis
NS3/4A	nonstructural protein 3/4A
OL	open-label
P2aR	pegylated interferon 2a plus ribavirin
P2bR	pegylated interferon 2b plus ribavirin
PR	pegylated interferon plus ribavirin
PP	per-protocol
QALY	quality-adjusted life-years
RBV	ribavirin
RCT	randomized controlled trial
RD	risk difference
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short-Form (36) Health Survey
SOF	sofosbuvir
SVR	sustained virologic response
SVR12	sustained virologic response 12 weeks after the end of treatment
TEL	telaprevir
WDAE	withdrawal due to adverse event

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.[1] Hepatitis C most commonly affects people older than 30 years of age, 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 2, 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-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 interferon-based treatment regimens.[8] Asunaprevir (ASV), a DAA against HCV, is an HCV nonstructural protein 3/4A (NS3/4A) serine protease inhibitor that inhibits viral replication. The recommended dose is 100 mg twice daily in combination with other drugs for genotype 1 and 4 CHC.

Indication
In combination with other agents for the treatment of chronic hepatitis C (CHC) in adult patients with hepatitis C virus (HCV) genotypes 1 or 4 and compensated liver disease, including cirrhosis.
Listing criteria requested by sponsor[a]
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G = genotype; HCV = hepatitis C virus; PR = pegylated interferon plus ribavirin.

[a] The listing request was submitted February 12, 2015. Due to delays in receiving Notice of Compliance, the asunaprevir submission was suspended and then reinitiated on March 15, 2016. The manufacturer has acknowledged that the treatment paradigm has shifted rapidly over this time period and it is now understood that a PR-based regimen would not be relevant in the Canadian setting, given the emergence of the new direct-acting antiviral agents.

The objective of this systematic review was to evaluate the beneficial and harmful effects of ASV in combination with other drugs for the treatment of CHC genotypes 1 and 4.

Results and Interpretation

Included Studies

Four open-label studies met the inclusion criteria, including one randomized controlled trial (RCT) (Study 031) and three uncontrolled studies (Hallmark DUAL, Hallmark NIPPON, and Hallmark QUAD). The patients enrolled had genotype 1b (DUAL, NIPPON, 031), genotype 1 or 4 (QUAD), and included treatment-naive (DUAL, 031), treatment-experienced (DUAL, NIPPON), and interferon-ineligible or -intolerant cohorts (DUAL, NIPPON). The sample size per treatment cohort ranged from 22 to 440 patients.

ASV was combined with daclatasvir (DCV) in three trials (DUAL, NIPPON, 031), and with DCV and pegylated interferon plus ribavirin (PR) in one trial (QUAD). The primary outcome in all studies was sustained virologic response 12 or 24 weeks after the end of treatment (SVR12 or SVR24). Study 031 assessed whether DCV + ASV was non-inferior to telaprevir (TEL) plus PR in terms of SVR12. Two trials were conducted in Japan (NIPPON, 031) and two were conducted in multiple countries in North and South America, Europe, and Asia (DUAL, QUAD). Key limitations included the lack of direct head-to-head comparison to alternative therapies. Limited data were available in patients with genotype 4 CHC or cirrhosis. Of note, despite the scientific limitations associated with uncontrolled study designs, these designs were considered adequate by Health Canada to grant regulatory approval.

Efficacy

Daclatasvir Plus Asunaprevir

DCV combined with ASV for 24 weeks achieved SVR12 rates between 81% and 90% among patients with genotype 1b CHC, and showed similar response rates regardless of the patients' prior treatment history, or presence of cirrhosis. In treatment-naive genotype 1b patients, DCV + ASV was non-inferior to TEL + PR in terms of SVR12 (89% versus 66%, per-protocol analysis) based on Study 031. Relapse rates ranged from 3% to 9% among genotype 1b patients who received DCV + ASV, and were lower than TEL + PR (19%). In the treatment-experienced genotype 1b patients who did not achieve SVR12, more patients had an on-treatment failure than a relapse.

Daclatasvir Plus Asunaprevir and PR

SVR12 rates exceeded 90% in treatment-experienced patients with genotype 1 or 4 CHC (93% and 98%, respectively) who received DCV/ASV + PR for 24 weeks, and were similar across subgroups based on fibrosis severity, genotype subtype, and prior treatment response. The reported relapse and on-treatment failure rates were low (≤ 4%).

Health-Related Quality of Life

Quality-of-life data were reported as exploratory outcomes in three studies. These data showed no clinically important changes in quality-of-life scores at the end of treatment, or 12 weeks after treatment, in patients who received an interferon-free regimen (DCV + ASV). Among patients who received an interferon-based regimen (TEL + PR or DCV/ASV + PR), quality-of-life scores decreased substantially on treatment, but returned to baseline values 12 weeks after the end of treatment.

Indirect Treatment Comparison

The manufacturer submitted indirect treatment comparisons for DCV + ASV in patients with genotype 1b CHC. Although DCV + ASV combinations were found to be comparable or superior to other treatments, the indirect treatment comparison excluded the interferon-free regimens that are the current standard of care for genotype 1 CHC. Even though it seems that most aspects one could consider critically appraising have been discussed satisfactorily (i.e., except for the few limitations), there is

current uncertainty as to the performance of matching-adjusted indirect comparison (MAIC) techniques for indirect treatment comparisons. This approach has not been empirically assessed in the peer-reviewed literature and its strengths and weaknesses still require investigation by the research community. CADTH undertook a Therapeutic Review that provided estimates of the comparative efficacy and safety of PR-based and interferon-free DAA regimens for CHC.[9] The CADTH Therapeutic Review reported that the rate of SVR12 was statistically significantly lower for DCV + ASV compared with ledipasvir/sofosbuvir (risk difference [RD] –7%) and was not statistically significantly different from sofosbuvir/ribavirin or ombitasvir/paritaprevir/ritonavir + dasabuvir in treatment-naive genotype 1b CHC patients.[9] In treatment-experienced genotype 1b patients, SVR12 was statistically significantly lower for DCV + ASV than ombitasvir/paritaprevir/ritonavir + dasabuvir (RD –18%) and not significantly different compared with ledipasvir/sofosbuvir.[9] Among treatment-experienced genotype 1 CHC patients, no statistically significant differences in SVR12 were detected between DCV/ASV + PR and other interferon-free DAA regimens.[9] These estimates were based largely on data from single-arm trials, and thus are associated with greater uncertainty than indirect treatment comparisons based on controlled trials.

Harms

The incidence of adverse events was high (> 73%) for all treatment groups, with headache, nausea, diarrhea, and fatigue reported most frequently. In the DUAL study, the incidence of any adverse event and of notable adverse events was similar for DCV + ASV and placebo during the initial 12-week double-blind treatment period. In Study 031, TEL + PR was associated with statistically significantly higher incidence of anemia, and clinically significant rash compared with DCV + ASV (rash: RD –12.6%; anemia: RD –47.7% for DCV + ASV versus TEL + PR). Patients who received DCV/ASV + PR also reported a higher frequency of rash, anemia, pruritus, and fatigue, which was consistent with the adverse event profile of interferon-based therapies. The incidence of serious adverse events was ≤ 7% in all treatment groups, including those who received PR. The proportion of patients who stopped treatment due to adverse events ranged from 1% to 7% among patients who received DCV + ASV or DCV/ASV + PR, and in Study 031 was higher among those administered TEL + PR (20%) than those on DCV + ASV (5%). DCV therapies compared favourably with other treatments in terms of withdrawals due to adverse events, based on the manufacturer-provided indirect treatment comparison; however, there is uncertainty in the results due to methodological limitations in the analyses. The CADTH Therapeutic Review found no statistically significant differences in rash or depression between DCV + ASV and other interferon-free DAA regimens, with two exceptions: DCV + ASV was associated with significantly less rash than ombitasvir/paritaprevir/ritonavir + dasabuvir with ribavirin, and a higher risk of depression than sofosbuvir plus ledipasvir in treatment-naive CHC patients.[9] DCV/ASV + PR was associated with a significantly higher risk of rash than interferon-free DAA regimens (except simeprevir/sofosbuvir) and a higher risk of anemia than ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir + dasabuvir, in treatment-experienced CHC patients.[9] Of note, the relatively small size and uncontrolled nature of the available studies for DAA-based regimens did not allow for a thorough assessment of harms in the CADTH Therapeutic Review.

Except for the first 12 weeks in the DUAL study, these trials were open-label, and so reporting of adverse events may potentially be biased by knowledge of the treatment received. This should be considered when interpreting the adverse event data, particularly Study 031.

Conclusions

Based on data from three uncontrolled studies and one RCT, ASV was associated with high rates of SVR12 when combined with DCV in patients with genotype 1b CHC, and combined with DCV + PR in patients with genotype 1 or 4 CHC infection. DCV + ASV was non-inferior to TEL + PR, based on one RCT in Japanese treatment-naive patients with genotype 1b CHC.

DCV + ASV combination therapy appears to be better tolerated than TEL + PR or DCV/ASV + PR, and was not associated with clinically important decreases in quality of life during treatment. However, the health-related quality of life data were exploratory.

The data were limited for some populations, specifically patients with genotype 4 CHC and patients with cirrhosis, due to the small numbers of patients treated.

No direct evidence was available on the comparative efficacy and safety of ASV + DCV or DCV + PR versus other DAA regimens or combinations currently in use in Canada. The CADTH Therapeutic Review provides some indirect evidence for ASV-based regimens; however, it must be interpreted considering the uncertainty associated with methods for synthesizing evidence from single-arm trials.

TABLE 1: SUMMARY OF RESULTS

Outcome	DUAL Genotype 1b DCV + ASV 24 weeks				NIPPON Genotype 1b DCV + ASV 24 weeks		Study 031 Genotype 1b Treatment-naive		QUAD DCV/ASV + PR 24 weeks	
	Treatment-naive Placebo	Treatment-naive DCV + ASV 24 weeks	Treatment-experienced	Ineligible for and/or intolerant to PR	Treatment-experienced	Ineligible for and/or intolerant to IFN	DCV + ASV 24 weeks	TEL + PR	Genotype 1 treatment-experienced	Genotype 4 treatment-experienced
SVR12										
n, N	NA	182/203	168/205	192/235	70/87	119/135	106/119[a]	65/99[a]	329/354	43/44
% (95% CI)		90% (85 to 94)	82% (77 to 87)	82% (77 to 87)	81% (72 to 89)	88% (83 to 94)	89% (84 to 95)[a]	66% (56 to 75)[a]	93% (90 to 96)	98% (93 to 100)
RD (95% CI)		NA	NA	NA	NA	NA	19% (9 to 28)[a]	REF	NA	NA
Relapse										
n, N	NA	5/189	7/174	12/204	6/76	11/129	9/115	16/85	8/337	0/43
%		3%	4%	6%	8%	9%	8%	19%	2%	0%
Serious adverse events										
n, N	1/102	12/205	11/205	16/235	4/87	9/135	5/119	6/111	22/398	
%	1%	6%	5%	7%	5%	7%	4%	5%	6%	
Discontinued treatment due to adverse event										
n, N	0/102	6/205	2/205	2/235	2/87	9/135	6/119	22/111	18/398	
%	0%	3%	1%	1%	2%	7%	5%	20%	5%	

ASV = asunaprevir; CHC = chronic hepatitis C virus; CI = confidence interval; DAA = direct-acting antiviral; DCV = daclatasvir; IFN = interferon; mITT = modified intention-to-treat; N = number of patients; NA = not applicable; PR = pegylated interferon plus ribavirin; RD = risk difference; REF = reference; SVR12 = sustained virologic response 12 weeks after the end of treatment.

[a] Per-protocol analysis reported; mITT analysis: DCV + ASV 89% (95% CI 84% to 95%); TEL + PR 62% (95% CI 53% to 71%), RD: 26% (95% CI 16% to 36%).

Source: Clinical Study Report,[10-13] Manns,[14] Kumada,[15] Jensen.[16]

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 (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] A total of 11,357 cases of hepatitis C (HCV) were reported in Canada in 2009, mostly due to injection drug use.[2] Hepatitis C most commonly affects people older than 30 years of age, 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.[1]

Of those infected, approximately 25% clear infection spontaneously (range 15% to 45%) and the remainder develop chronic infection.[17-19] 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] Male gender, alcohol use, HIV coinfection, obesity, and increasing age are associated with an increased risk of liver disease progression.[3,20] 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]

Patients have expressed the need for new treatments with higher cure rates, better side-effect profiles, and reduced treatment burden. Alternative treatment options are needed particularly for those with genotypes 2, 3, and 4. There is also a need to identify optimal treatment strategies for patients who have had an inadequate response to first-line treatments. In addition, treatments must be accessible and affordable for patients.

1.2 Standards of Therapy

The treatment paradigm for CHC infection continues to evolve rapidly. Prior to 2011, pegylated interferon plus ribavirin (PR) was the gold standard therapy for patients with CHC infection. Approximately half of patients infected with genotype 1 HCV could expect to achieve sustained virologic response (SVR) with a 48-week course of PR therapy.[21] In recent years, greater understanding of the hepatitis C viral replication cycle has resulted in the development of direct-acting antiviral (DAA) agents that target several types of nonstructural proteins used to support viral replication (Table 3). These regimens resulted in a further advance in SVR rates as compared with PR regimens that did not include a DAA. The first DAAs approved in Canada (boceprevir [BOC], telaprevir [TEL], simeprevir [SIM], and sofosbuvir [SOF]) were used in combination with PR in patients with genotype 1 CHC (Table 4). A major limitation to PR-based treatment regimens has been the tolerability. A number of interferon-free DAA regimens have now been approved in Canada for genotype 1, 2, 3, and 4 CHC, with improved tolerability, high response rates, and shorter treatment durations (Table 5).[21] The treatment paradigm for hepatitis C has been shifting rapidly as new evidence emerges. Use of the protease inhibitors, BOC and TEL, has been replaced by newer DAA regimens. TEL is no longer marketed in Canada and BOC will soon be discontinued as well.[8] The recommendations from the CADTH Canadian Drug Expert Committee (CDEC) on the CADTH Therapeutic Review *Drugs for Chronic Hepatitis C Infection* was the use of ledipasvir (LDV)/SOF and ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin as preferred regimens for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis

status; daclatasvir (DCV) + SOF for 12 weeks for patients with CHC genotype 3 infection, without cirrhosis; SOF and ribavirin (RBV) for 24 weeks for patients with CHC genotype 3 infection, with cirrhosis; and SOF + PR for 12 weeks in treatment-naive patients with CHC genotype 4 infection who are non-cirrhotic.[22] Of note, asunaprevir (ASV) was not commercially available at the time of the publication of the CADTH Therapeutic Review and thus no recommendations were made with regard to this drug.

1.3 Drug

ASV, a DAA against HCV, is an HCV nonstructural protein 3/4A (NS3/4A) serine protease inhibitor that inhibits viral replication. The recommended dose is 100 mg twice daily in combination with other agents for genotype 1 and 4 CHC (Table 2).

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TABLE 2: ASUNAPREVIR DOSING BY HEPATITIS C VIRUS GENOTYPE

Population	Regimen	Duration
Genotype 1b Treatment-naive[a] or treatment-experienced,[b] with or without compensated cirrhosis	DCV 60 mg daily + ASV 100 mg twice daily	24 weeks
Genotype 1 or 4 Treatment-naive[a,c] or treatment-experienced,[b] with or without compensated cirrhosis	DCV 60mg daily + ASV 100 mg twice daily, PR as per labels	24 weeks

ASV = asunaprevir; DCV = daclatasvir; G = genotype; HCV = hepatitis C virus; PR = pegylated interferon plus ribavirin.
[a] Treatment-naive is defined as no prior exposure to any interferon, ribavirin, or other approved or experimental HCV-specific direct-acting antiviral agent at the time of treatment initiation.
[b] Treatment-experienced is defined as those who failed prior therapy with an interferon-based regimen, including null or partial response, or are intolerant to or ineligible for interferon-based therapy.
[c] Clinical trial experience with the DCV/ASV + PR regimen in treatment-experienced patients is extrapolated to treatment-naive patients.
Source: Sunvepra product monograph.[23]

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.	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 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.	Fatigue, headache
Ombitasvir/ paritaprevir/ ritonavir and dasabuvir ± 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. Dasabuvir: non-nucleoside polymerase inhibitor encoded by the NS5B gene, which is essential for replication of the viral genome.	Treatment of adults with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.	Fatigue, headache, nausea, pruritus, and 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 chronic hepatitis C virus (CHC) genotype 4 infection in adults without cirrhosis.	Fatigue, headache, nausea, pruritus, and 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.	headache and fatigue

Drug	Mechanism of Action	Health Canada Indication	Serious Side Effects/Safety Issues
		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 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, and 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 and fatigue

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral; HCV = hepatitis C virus; NS = nonstructural protein; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy.
Source: Product monographs.[23-30]

TABLE 4: DOSING REGIMENS FOR DIRECT-ACTING ANTIVIRALS USED IN COMBINATION WITH PEGYLATED INTERFERON AND 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)
Genotype 4	Similar to genotype 1 dosing	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)

CHC = chronic hepatitis C virus; 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.[23,25,27]

TABLE 5: RECOMMENDED DOSING FOR INTERFERON-FREE DIRECT-ACTING ANTIVIRAL REGIMENS

Treatment Regimen	Genotype 1	Genotype 4
Simeprevir/Sofosbuvir	Simeprevir 150 mg capsule once daily with sofosbuvir 400 mg tablet, once daily for 12 weeks Treatment-naive, prior relapse patients, and prior non-responder 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 treatment-naive and non-cirrhotic treatment-experienced CHC patients with genotype 1 infection who are ineligible to receive an interferon-based regimen	
Ledipasvir/sofosbuvir	Sofosbuvir 400 mg fixed-dose combination tablet with 90 mg ledipasvir once daily for 12 weeks (24 weeks for treatment-experienced patients with cirrhosis; 8 weeks can be considered for treatment-naive patients with HCV RNA > 6 million IU/mL)	
Ombitasvir/ Paritaprevir/Ritonavir and Dasabuvir	Two fixed-dose ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg 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 fixed-dose ombitasvir 12.5 mg / paritaprevir 75 mg / ritonavir 50 mg tablets taken once daily (in the morning) for 12 weeks combined with ribavirin. Ombitasvir/paritaprevir/ritonavir administered without RBV for 12 weeks may be considered for treatment-naive patients who cannot take or tolerate ribavirin
Elbasvir/grazoprevir	One fixed-dose elbasvir 50 mg/grazoprevir 100 mg 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 fixed-dose elbasvir 50 mg/ grazoprevir 100 mg 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 (treatment-naive, or treatment-experienced)[a]	

Treatment Regimen	Genotype 1	Genotype 4
	Without cirrhosis 12 weeks **With cirrhosis** 24 weeks	
Daclatasvir/ Asunaprevir	**Genotype 1b** Daclatasvir 60 mg tablet daily plus asunaprevir 100 mg twice daily for 24 weeks (treatment-naive or treatment-experienced, with or without compensated cirrhosis)[a]	

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; RNA = ribonucleic acid; 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.[23-30]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ASV in combination with other drugs for the treatment of CHC genotypes 1 and 4.

2.2 Methods

All manufacturer-provided trials considered pivotal in the manufacturer's submission[31] and the draft product monograph[23] were included in the systematic review. Other phase 3 studies were selected for inclusion based on the selection criteria presented in Table 6.

TABLE 6: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with CHC genotypes 1 to 4 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
Intervention	• Daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily (genotype 1b) • Daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily plus PR (genotype 1, 4)
Comparators	**Genotype 1** • ledipasvir/sofosbuvir • ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin • boceprevir in combination with PR • telaprevir in combination with PR • simeprevir in combination with PR • sofosbuvir in combination with PR • sofosbuvir in combination with ribavirin • simeprevir plus sofosbuvir • placebo in combination with PR • placebo or no treatment **Genotype 4** • sofosbuvir in combination with PR • placebo in combination with PR • placebo/no treatment
Outcomes	**Key efficacy outcomes:** • Sustained virologic response • Relapse • HRQoL • Mortality (all cause and liver-related) **Other efficacy outcomes:** • Hepatic-related morbidity outcomes (e.g., histological changes, hepatocellular carcinoma, liver failure, liver transplant) **Harms outcomes:** • SAE, WDAE, AE Harms of special interest (rash, fatigue, anemia, neutropenia, pruritus, depression)

Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; CHC = chronic hepatitis C; DAA = direct-acting antiviral; DB = double-blind; HRQoL = health-related quality of life; PR = pegylated interferon plus ribavirin; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

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

The original literature search was conducted in 2015 as part of the review of Daklinza by the CADTH Common Drug Review (CDR) (see Daklinza Clinical Report for methods). Due to a delay in receiving Notice of Compliance for asunaprevir, the CDR review was suspended and reinitiated on March 15, 2016. An update to the literature search was conducted according to the methods described below.

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 Sunvepra (asunaprevir).

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

The initial search was completed on March 18, 2016. Regular alerts were established to update the search until the meeting of CDEC on June 15, 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), Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 7 and Table 8; excluded studies (with reasons) are presented in APPENDIX 3.

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 7 and Table 8, and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

From the Daklinza literature search conducted in 2015, a total of four clinical trials met the inclusion criteria: Hallmark DUAL,[11,14] Hallmark NIPPON,[10,15] Study 031,[13] and Hallmark QUAD.[12,16] One supplementary data source was identified as well.[31] Based on the updated literature search conducted in 2016, no new clinical trials were identified that met the inclusion criteria; however, one additional relevant publication was found.[32]

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

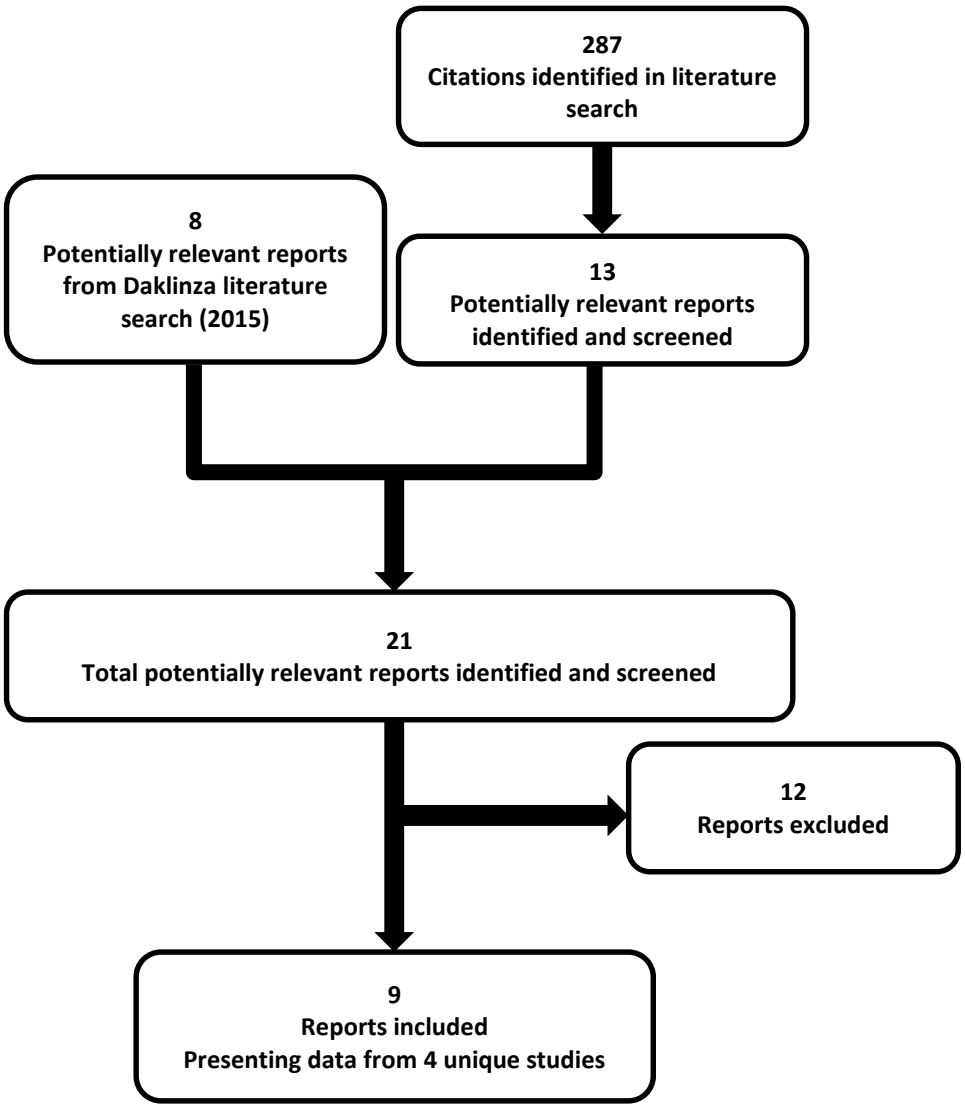


TABLE 7: DETAILS OF INCLUDED STUDIES – DACLATASVIR PLUS ASUNAPREVIR

		Hallmark DUAL AI447-028 (Pivotal)		Hallmark NIPPON AI447-026 (Pivotal)	AI447-031	
DESIGNS & POPULATIONS	**Study Design**	DB RCT	Non-randomized, OL, 2 parallel groups	Non-randomized, OL, 2 parallel groups	RCT	Non-randomized, OL, single group[a]
	Locations	N. America, S. America, Europe, Asia		Japan	Japan	
	Randomized / Enrolled (N)	307	440	222	236	22
	Inclusion Criteria	• treatment-naive • genotype 1b CHC • age ≥ 18 years	• genotype 1b CHC • age ≥ 18 years who were either: • Prior non-responder to PR (null or partial response) (cohort 1), or • Ineligible for and/or intolerant to PR (treatment-naive or experienced) (cohort 2)	• genotype 1b CHC age 20 to 70 years who were either: • non-responders (null or partial responders) to interferon alfa or beta and ribavirin (cohort 1),b or • intolerant of or ineligible to receive interferon-based therapy (cohort 2)[c]	• genotype 1b CHC • age 20 to 70 years • treatment-naive • eligible to receive IFN-based therapy	• genotype 1b CHC • age 20 to 75 years • relapsed following IFN-based therapy
	Exclusion Criteria	• decompensated liver disease • hepatitis B or HIV • HCC or other cancer • prior exposure to DAA • recent substance abuse • moderate to severe depression • severe psychiatric disorder • CrCl < 50 mL/min		• hepatitis B or HIV • HCC or other cancer • prior exposure to NS5A or NS3 protease inhibitors • decompensated liver disease • recent substance abuse • creatinine > 1.8 x upper limit of normal	• hepatitis B or HIV • cirrhosis • history of cancer • decompensated liver disease • recent substance abuse • CrCl < 50 mL/min	• relapsed following TEL + PR therapy • hepatitis B or HIV • cirrhosis • history of cancer • decompensated liver disease • recent substance abuse • CrCl < 50 mL/min
DRUGS	**Intervention**	DCV 60 mg daily plus ASV 100 mg twice daily x 12 weeks (DB), then same regimen OL for 12 weeks	DCV 60 mg daily plus ASV 100 mg twice daily x 24 weeks	DCV 60 mg daily plus ASV 100 mg twice daily x 24 weeks	DCV 60 mg daily plus ASV 100 mg twice daily x 24 weeks	DCV 60 mg daily plus ASV 100 mg twice daily x 24 weeks
	Comparator(s)	Placebo x 12 weeks, then enrolled in another DCV plus ASV clinical trial	None	none	TEL 750 mg 3 times daily plus PR x 12 weeks, then PR x 12 weeks[d,e]	none

		Hallmark DUAL AI447-028 (Pivotal)		Hallmark NIPPON AI447-026 (Pivotal)	AI447-031	
DURATION	**Phase**	3		3	3	
	DB	12 weeks	NA	NA	NA	NA
	OL	12 weeks	24 weeks	24 weeks	24 weeks	24 weeks
	Follow-up	24 weeks	24 weeks	24 weeks	24 weeks	24 weeks
OUTCOMES	**Primary End Point**	SVR12	SVR12	SVR24	SVR12	--
	Other End Points	Relapse Harms	Relapse Harms	SVR12 Relapse Harms	Hgb < 10 g/dL Rash Relapse SF-36 Harms	SVR12 Relapse Harms
NOTES	**Publications**	Manns[14]		Kumada[15]	Kumada[32]	

ASV = asunaprevir; CHC = chronic hepatitis C; CrCl = creatinine clearance; DB = double-blind; DAA = direct-acting antiviral; DCV = daclatasvir; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; Hgb = hemoglobin; IFN = interferon; NA = not applicable; NS = nonstructural protein; OL = open-label; PR = pegylated interferon plus ribavirin; RCT = randomized controlled trial; SF-36 = Short-Form (36) Health Survey; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; TEL = telaprevir.

[a] The non-randomized cohort of this non-pivotal trial did not meet the inclusion criteria for the systematic review, and thus has not been summarized in the body of this report. However, data from this cohort are reported in APPENDIX 6.

[b] Patients who were null or partial responders to previous PR or IFN-beta/ribavirin therapy were defined as having never attained an undetectable HCV RNA level after at least 12 weeks of therapy. Null responders included patients who never attained at least a 2-log10 decrease from baseline in HCV RNA levels at week 12, and partial responders never achieved undetectable HCV RNA levels after 12 weeks of therapy.

[c] Patients ineligible for IFN-based therapy, but potentially eligible for enrolment in this study, were treatment-naive and considered poor candidates for IFN-based therapy because of medical complications including anemia, neutropenia, thrombocytopenia, depression, advanced age (65 years), or other conditions deemed not suitable for IFN-based therapy by the investigator, including hypertension, diabetes mellitus, autoimmune disease, and abnormal thyroid function. Patients intolerant to IFN-based therapy had received IFN-based therapy for less than 12 weeks and previously discontinued from therapy due to toxicities associated with interferon or ribavirin.

[d] Pegylated interferon alfa 2b 1.5 mcg/kg subcutaneously once weekly plus weight-based ribavirin, by mouth.

[e] Patients who met on-treatment virologic failure criteria could receive rescue therapy consisting of DCV/ASV + PR for an additional 24 or 48 weeks.

Note: One additional report was included (CADTH Common Drug Review submission Sunvepra[31]).

Source: Manns,[14] Kumada,[15] Kumada,[32] CSRs.[10,11,13]

TABLE 8: DETAILS OF INCLUDED STUDIES — DACLATASVIR PLUS ASUNAPREVIR PLUS PR

		Hallmark QUAD AI447-029 (Pivotal)
DESIGNS & POPULATIONS	**Study Design**	OL, non-randomized (2 cohorts)
	Locations	N. America, S. America, Europe, Asia
	Enrolled (N)	398
	Inclusion Criteria	– genotype 1 or 4 CHC – age ≥ 18 years – prior null or partial response to PR
	Exclusion Criteria	– prior DAA therapy – coinfection with HIV or hepatitis B – hepatic decompensation – HCC or other cancer – ineligible to receive PR – recent substance abuse – CrCl < 50 mL/min
DRUGS	**Intervention**	DCV 60 mg daily + ASV 100 mg twice daily pegylated interferon alfa 180 mcg/week SC + weight-based ribavirin (< 75 kg = 1,000 mg or ≥ 75 kg = 1,200 mg mg/day, oral) x 24 weeks
	Comparator(s)	None
DURATION	**Phase**	3
	OL	24 weeks
	Follow-up	24 weeks
OUTCOMES	**Primary End Point**	SVR12
	Other End Points	SVR24 Relapse SF-36 Harms
NOTES	**Publications**	Jensen[16]

ASV = asunaprevir; CHC = chronic hepatitis C; CrCl = creatinine clearance; DAA = direct-acting antiviral; DCV = daclatasvir; HCC = hepatocellular carcinoma; OL = open label; PR = pegylated interferon plus ribavirin; SC = subcutaneous; SF-36 = Short-Form (36) Health Survey; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment.
Source: Jensen,[16] Clinical Study Report.[12]

3.2 Included Studies

3.2.1 Description of Studies

A total of four trials met the inclusion criteria: three pivotal clinical trials (DUAL, NIPPON, QUAD) and one RCT (Study 031) (Table 7, Table 8). The primary outcome in all trials was SVR12 or SVR24.

Three trials evaluated DCV + ASV for 24 weeks in patients with genotype 1b CHC (DUAL, NIPPON, 031).

- The Hallmark DUAL study had a double-blind randomized controlled portion used to assess the safety of DCV + ASV over a 12-week treatment period. In the DUAL study, treatment-naive patients were randomized 2:1 to receive either DCV + ASV or matching placebo for 12 weeks. After 12 weeks, patients in the DCV + ASV group continued on open-label therapy for a total of 24 weeks' treatment. Patients in the placebo group were enrolled in another DCV + ASV trial. The DUAL trial also included two non-randomized cohorts of patients with genotype 1b who were either non-responders to prior PR therapy or were ineligible or intolerant of PR therapy.

- The Hallmark NIPPON study was an open-label non-randomized clinical trial that enrolled genotype 1b patients who were either non-responders to prior interferon therapy or were ineligible or intolerant of interferon-based therapy.
- Study 031 was an open-label RCT. Treatment-naive patients with genotype 1b CHC who were eligible for interferon-based therapy were randomized 1:1 to DCV + ASV for 24 weeks or to TEL + PR for 12 weeks, then PR for 12 weeks.

One non-randomized open-label trial evaluated DCV/ ASV + PR for 24 weeks in patients with genotype 1 or 4 CHC who had prior null or partial response to PR therapy (QUAD).

One study (Study 031) included an additional cohort that did not meet this review's inclusion criteria and these groups have not been summarized in this report. The non-randomized cohort of patients with a history of relapse in Study 031 were excluded from the systematic review but have been summarized in APPENDIX 6.

3.2.2 Populations

a) Inclusion and exclusion criteria

The trials enrolled adults with CHC genotype 1b (DUAL, NIPPON, 031), genotype 1 or 4 (QUAD). Two trials enrolled patients who were treatment-naive (DUAL, 031), three trials included treatment-experienced patients (DUAL, NIPPON, QUAD), and two trials enrolled patients who were interferon-ineligible or -intolerant (DUAL, NIPPON). In the DUAL, NIPPON and QUAD studies, the treatment-experienced patients had a prior null or partial response to PR.

All trials excluded patients with decompensated liver disease, hepatitis B or HIV coinfection, malignancy, or recent substance abuse.

b) Baseline characteristics

Across the studies, the median age ranged from 52 to 64 years of age, and the proportion of males ranged from 28% to 75% (Table 9). The proportion of patients with cirrhosis (or Meta-analysis of Histological Data in Viral Hepatitis [METAVIR] fibrosis stage F4) varied between cohorts within trials and between trials (range 5% to 47%); however, the baseline characteristics between the randomized treatment groups in DUAL and Study 031 appear to be similar. As most studies were non-randomized, differences between treatment groups within the same trial were expected.

TABLE 9: SUMMARY OF BASELINE CHARACTERISTICS

	Hallmark DUAL				Hallmark NIPPON		Study 031		Hallmark QUAD	
	Placebo	**DCV + ASV 24 weeks**			**DCV + ASV 24 weeks**		**DCV + ASV 24 weeks**	**TEL + PR 12 weeks, PR 12 weeks**	**DCV/ASV + PR 24 weeks**	
	Treatment-naive	**Treatment-naive**	**Treatment-experienced**	**Ineligible/ intolerant**	**Treatment-experienced**	**Ineligible/ intolerant**	**Treatment-naive**		**Treatment-experienced genotype 1**	**Treatment-experienced genotype 4**
N	102	205	205	235	87	135	119	111	354	44
Age (years), median (range)	54 (22 to 83)	55 (20 to 79)	58 (23 to 77)	60 (24 to 77)	60 (42 to 74)	64 (24 to 75)	57 (20 to 70)	56 (25 to 70)	54 (19 to 79)	52 (20 to 71)
Male, n (%)	54 (53)	101 (49)	111 (54)	98 (42)	39 (45)	38 (28)	48 (40)	54 (49)	240 (68)	33 (75)
HCV genotype, n (%)										
Genotype 1a									176 (50)	
Genotype 1b	102 (100)	205 (100)	205 (100)	235 (100)	87 (100)	135 (100)	119 (100)	111 (100)	178 (50)	
Genotype 4										44 (100)
Cirrhosis or METAVIR F4, n (%)	16 (16)	33 (16)	63 (31)	111 (47)	11 (13)	11 (8)	6 (5)	13 (12)	73 (21)	20 (46)
Baseline HCV RNA, log_{10} IU/mL, mean (SD)	6.3 (0.6)	6.2 (0.8)	6.5 (0.5)	6.4 (0.7)	6.8 (0.5)	6.6 (0.6)	6.8 (0.6)	6.8 (0.7)	6.5 (0.5)	6.1 (0.5)
Previous response to HCV treatment	NA	NA		NA		NA	NA	NA		
Relapse/breakthrough			2 (1)		0					
Partial response			84 (41)		36 (41)				120 (34)	10 (23)
Null response			119 (58)		48 (55)				234 (66)	34 (77)
Other			0		3 (3)					
Prior HCV treatment	NA	NA					NA	NA		
IFN regimen			205 (100)	170 (72)	87 (100)	35 (26)			354 (100)	44 (100)
DAA regimen										
Other										
IFN eligibility status	NA	NA	NA		NA		NA	NA		
Ineligible				143 (61)[a]		100 (74)				
Intolerant				170 (72)[a]		35 (26)				

ASV = asunaprevir; DAA = direct-acting antiviral; DCV = daclatasvir; HCV = hepatitis C virus; IFN = interferon; METAVIR = Meta-analysis of Histological Data in Viral Hepatitis; NA = not applicable; NR = not reported; PR = pegylated interferon plus ribavirin; RNA = ribonucleic acid; SD = standard deviation.

[a] 80 patients (34%) were both ineligible and intolerant to IFN therapy.

Source: Manns,[14] Kumada,[15] Jensen,[16] Clinical Study Report.[10-13]

3.2.3 Interventions

In all trials, the dose of ASV was 100 mg twice daily combined with DCV 60 mg daily (24 weeks). In the QUAD study, patients also received pegylated interferon alfa-2a (180 mcg subcutaneously per week) and weight-based ribavirin (< 75 kg: 1,000 mg daily; ≥ 75 kg: 1,200 mg daily). Study 031 also included a control group that received TEL + PR for 12 weeks, then PR for 12 weeks. TEL was administered as 750 mg three times daily, pegylated interferon alfa-2b 1.5 mcg/kg per week, and weight-based RBV (600 mg to 1,000 mg per day).

In the DUAL study, treatment-naive patients were randomized to receive either DCV + ASV or matching placebo for 12 weeks to examine treatment-related harms. After 12 weeks, patients in the placebo group were entered into another trial and those in the DCV + ASV group received another 12 weeks of open-label treatment.

In Study 031 and NIPPON, those who met predefined futility criteria were eligible to receive rescue therapy (DCV/ASV + PR) for 24 weeks to 48 weeks.

3.2.4 Outcomes

In the DUAL, 031, and QUAD studies, the primary outcome was SVR12 and in NIPPON it was SVR24. Other outcomes reported were the proportion of patients with relapse, on-treatment failure, quality of life, and adverse events.

In the trials, HCV RNA levels were collected weekly for the first two weeks, then every two weeks during treatment, at the end of treatment, and at post-treatment weeks 4, 12, and 24.

SVR12 was defined as HCV RNA levels less than the lower limit of quantification (LLOQ), either detectable or undetectable, 12 weeks after the end of treatment (Study 031, DUAL, QUAD, NIPPON).

SVR24 was defined as HCV RNA levels < LLOQ, either detectable or undetectable, 24 weeks after the end of treatment (NIPPON, QUAD, 031).

Relapse defined as HCV RNA measurement greater or equal to the LLOQ (25 IU/mL) post-treatment following an undetectable HCV RNA measurement at the end of treatment. The relapse rate was calculated using the number of patients who achieved undetectable HCV RNA levels at the end of treatment in the denominator. On-treatment failure included patients who had detectable HCV RNA levels at the end of treatment, including those who met the futility criteria to stop therapy or had a viral breakthrough during treatment.

Quality of life was reported as an exploratory outcome in three trials using generic health assessment questionnaires. The Short-Form (36) Health Survey (SF-36) was used in the QUAD and 031 studies. In Study 031 and QUAD, scores for the eight SF-36 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health) were reported (range 0 to 100). In general use of the SF-36, a change in 2 to 4 points in each domain indicates a clinically meaningful improvement as determined by the patient (APPENDIX 5).

Harms

An adverse event was defined as any new, untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered an investigational product. An adverse event could be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease

temporally associated with the use of investigational product, whether or not considered related to the investigational product. Adverse events that occurred during the treatment period were reported.

A serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, led to a congenital anomaly or birth defect, or was an important medical event that may not require hospitalization but may have jeopardized the patient or required intervention.

A composite of rash-related adverse events was reported, based on a predefined list of *Medical Dictionary for Regulatory Activities* (MedDRA)-preferred terms.

Harms-related secondary outcomes were included in Study 031:

- Proportion of patients with decline in hemoglobin to < 100 g/L during the first 12 weeks of treatment
- Proportion of patients with rash-related dermatologic events, defined as permanent discontinuation of any study drugs due to rash; grade 3 or 4 rash (according to Division of Autoimmune Immunodeficiency Disorders grading system); or rash that met the criteria for serious adverse events, reported during the first 12 weeks of treatment.

3.2.5 Statistical Analysis

In the DUAL, NIPPON, and QUAD studies, two-sided 95% confidence intervals (CIs) for SVR rates were computed using normal approximations to the binomial distribution. Those with missing data were classified as having no response at that visit. In Study 031 and NIPPON, those who required rescue therapy were classified as non-responders. No between-group statistical comparisons were conducted in the QUAD or NIPPON studies. Sample size calculations are listed in APPENDIX 9.

In Study 031, differences in SVR rates between DCV + ASV and TEL + PR were estimated using a stratum-adjusted Mantel–Haenszel approach stratified by IL28B (TT or non-TT). If the lower bound of the 95% CI for the difference in SVR12 rates was > –15%, it was inferred that DCV + ASV was non-inferior to TEL + PR. No information was provided as to how the non-inferiority margin was established in terms of its clinical and statistical implications. The primary analysis used modified intention-to-treat (mITT), the supportive analysis used observed cases, and the second sensitivity analysis used the per-protocol (PP) population. A sequential testing procedure was employed for testing the primary and key secondary end points:

1) The assessment for the non-inferiority for the difference in SVR12 rates between DCV + ASV and TEL + PR
2) The superiority test of the difference between DCV + ASV versus TEL + PR in proportion of patients with hemoglobin < 100g/L through week 12
3) The superiority test of the difference between DCV + ASV versus TEL + PR in proportion of patients with rash-related dermatologic events of special interest reported through week 12.

Testing was stopped if the preceding tests were not statistically significant. For each of the tests, the nominal type I error rate was set at 5% (two-sided).

In the DUAL study, the SVR12 rate for the treatment-naive cohort was compared with historical results for TEL + PR. The primary objective was to show that the lower bound of the 95% CI for DCV + ASV was greater than 68%. No statistical testing was performed comparing DCV + ASV to the historical controls.

For the treatment-experienced and interferon-ineligible and/or intolerant cohorts, SVR12 rates were reported, but no comparison was made with historical controls.

Quality of life was reported as an exploratory outcome in the QUAD and 031 trials, and descriptive data were reported only (i.e., no statistical inference).

Analysis populations
In all trials, the efficacy and safety analyses were based on an mITT population that included all enrolled patients who had received at least one dose of study medication, rather than all patients enrolled or randomized in the trial.

In Study 031, the PP population consisted of those randomized and treated patients without relevant protocol deviations in the treatment-naive cohort.

The safety data exclude any adverse events that occurred after patients started rescue treatment in Study 031 and NIPPON.

3.3 Patient Disposition

Between 8% and 23% of patients enrolled in the trials did not enter the treatment phase. The most common reason stated for this was that the patient no longer met the inclusion criteria (Table 10). The proportion of patients who did not complete therapy ranged from 7% to 16% of those administered DCV + ASV, and 5% given DCV/ASV + PR. In Study 031, 32% of patients on TEL + PR discontinued compared with 9% on DCV + ASV. In this open-label study, 5% of those in the TEL group and none in the DCV + ASV group withdrew after treatment allocation. In Study 031, 20% versus 5% discontinued due to adverse events, and 9% versus 3% due to lack of efficacy in the TEL versus DCV + ASV groups, respectively. Lack of efficacy or adverse events were the most commonly reported reasons for discontinuation in the DUAL, NIPPON, and QUAD studies.

TABLE 10: PATIENT DISPOSITION

	Hallmark DUAL Genotype 1b				Hallmark NIPPON Genotype 1b		Study 031 Genotype 1b		Hallmark QUAD Genotype 1 and 4	
	Placebo	**DCV + ASV 24 weeks**			**DCV + ASV 24 weeks**		**DCV + ASV 24 weeks**	**TEL + PR 12 weeks, then PR 12 weeks**	**DCV/ASV + PR 24 weeks**	
	Treatment-naive	**Treatment-naive**	**Treatment-experienced**	**Ineligible/ intolerant**	**Treatment-experienced**	**Intolerant/ ineligible**	**Treatment-naive**	**Treatment-naive**	**Treatment-experienced**	
Screened, N	NR				NR		NR		496	
Randomized/Enrolled, N (%)	975[a]				259[b]		256[c]		NR	
Enrolled and Treated, N	307				222 (86%)		236 (92%)		398 (80%)	
	102	205	205	235	87	135	119	111	G1 354	G4 44
Discontinued, N (%)	0	15 (7)	28 (14)	27 (11)	14 (16)	14 (10)	11 (9)	36 (32)	19 (5)	0
Adverse event		6 (3)	2 (1)	2 (1)	2 (2)	9 (7)	6 (5)	22 (20)	7 (2)	0
Lack of efficacy		8 (4)	26 (13)	20 (9)	11 (13)	4 (3)	4 (3)	10 (9)	11 (3)	0
Patient request		0	0	1 (< 1)	1 (1)	1 (1)	0	4 (4)	0	0
Lost to follow-up		1 (< 1)	0	0	0	0	0	0	1 (< 1)	0
Withdrew consent		0	0	4 (2)	0	0	0	0	0	0
Pregnancy		0	0	0	0	0	1 (1)	0	0	0
mITT, N	NA[d]	203	205	235	87	135	119	111	354	44
Per-protocol, N	NR	NR	NR	NR	NR	NR	119	99	NR	NR
Safety, N	102	205	205	235	87	135	119	111	354	44

ASV = asunaprevir; DCV = daclatasvir; G1 = genotype 1; G2 = genotype 2; mITT = modified intention-to-treat; N = number of patients; NA = not applicable; NR = not reported; PR = pegylated interferon plus ribavirin.

[a] 227 (23.3%) patients were enrolled but did not enter the treatment period. The most common reasons for not entering the treatment period were that the patient no longer met the study criteria (192 patients) or the patient withdrew consent to participate (29 patients).

[b] 35 patients enrolled but did not enter the treatment period because they did not meet the study criteria during the screening period (33 patients) or they withdrew consent (2 patients). Two additional patients who had initially met study entry criteria during screening were never treated because of withdrawal of consent and for no longer meeting study entry criteria.

[c] 20 patients no longer met the inclusion criteria and did not receive treatment.

[d] Placebo group was assessed for harms only.

Source: Manns,[14] Kumada,[15] Jensen,[16] Clinical Study Report.[10-13]

3.4 Exposure to Study Treatments

The median duration of DCV + ASV therapy was 24.0 weeks in all cohorts in the DUAL, NIPPON, QUAD, and 031 clinical trials.

3.5 Critical Appraisal

3.5.1 Internal Validity

One trial (031) randomized patients to treatment groups using appropriate methods and allocation concealment (computer-generated randomization sequence and an interactive voice or Web response system). A second trial (DUAL) had a randomized, double-blind component, in which patients were allocated (using an interactive voice response system) to DCV + ASV or matching placebo. The remaining two included studies were non-randomized trials (QUAD, NIPPON). The DUAL trial also included two non-randomized cohorts.

All trials were open-label, except the treatment-naive cohort in the DUAL study, in which patients and investigator sites were blinded to treatment assignment (DCV + ASV or placebo) until week 12 when treatment-emergent adverse events were assessed. Study 031 masked HCV RNA results from patients and investigators for samples collected up to the time of post-treatment week 12 analysis. In these open-label trials, the primary outcome and other measures related to viral load are objective and are unlikely to be affected by the open-label design; however, the reporting of adverse events and quality of life could potentially be biased by knowledge of treatment received. In addition, patients' willingness to continue therapy may be influenced by knowledge of the treatment received. The degree to which this occurred in the trials is unknown; however, the observed rates of discontinuation (0% to 14%) are numerically higher than discontinuation rates observed in trials for other interferon-free regimens, such as LDV/SOF (0% to 4.1%) or ombitasvir/ paritaprevir/ritonavir + dasabuvir ± ribavirin (0% to 5.4%).[33,34] Without a direct comparison, no conclusion can be made regarding the differences observed between trials when comparing these interferon-free DAA regimens. These rates may also be sensitive to the relatively small sample sizes of the treatment arms.

Study 031 used a non-inferiority design to compare DCV + ASV to TEL + PR. The analysis of SVR12, the primary outcome, was based on the mITT population, not the PP population, which is generally more conservative in a non-inferiority study. This is of particular significance considering the tolerability issues associated with interferon-based regimens and the differences in withdrawal rates observed (9% versus 32% for DCV + ASV versus TEL + PR). There was no explanation provided for the selection of the –15% non-inferiority margin. The TEL group's PR treatment duration was fixed at 24 weeks and did not follow the response-guided dosing recommended in the Canadian product monograph. Thus, a portion of patients may have received suboptimal therapy according to Canadian standards. This would include the 13 patients (12%) with cirrhosis, and potentially the 44 patients (40%) who did not achieve an extended rapid virologic response (undetectable HCV RNA levels at week 4 and 12).

Because all trials (except Study 031) were uncontrolled, the efficacy of DCV therapy compared with existing treatments cannot be established directly from the studies. Although the DUAL trial compared SVR rates to a historical control, without a concurrent, randomized control group, we cannot be assured that potential confounders are equally distributed and the cohorts are comparable aside from the intervention. The historical control rate comes from a different dataset in a different time, so differences in clinical standards outside of the intervention may have an impact on results. Moreover, no statistical testing was performed, and thus no conclusions can be drawn. Despite the scientific limitations associated with historical control study designs, these designs were considered adequate by Health Canada and the FDA to grant regulatory approval. Study 031 is the only RCT included in the

review that directly compared DCV + ASV to TEL + PR. However, that study suffered from potential bias due to disproportionate discontinuation rates (9% versus 32%), primarily as a result of lack of efficacy or adverse events.

Due to the small number of patients enrolled with genotype 4 in QUAD (N = 44), there were limited data on the efficacy of DCV/ASV + PR in genotype 4 CHC. The findings from this cohort should be interpreted with caution.

3.5.2 External Validity

A considerable proportion of patients enrolled in the trials but didn't enter the treatment phase. The reasons are unknown. This may largely compromise the generalizability of the results on SVR to the target population. All trials excluded patients with decompensated liver disease, HIV or hepatitis B coinfection, reduced kidney function, malignancy, and recent substance abuse; therefore, the generalizability of the results of the included studies to these populations is unknown. Furthermore, no data were available on other subgroups of interest, such as patients with liver transplantation or renal insufficiency, and limited data were available for patients with cirrhosis.

The TEL + PR dosage regimen utilized in Study 031 was not consistent with Canadian recommendations. In addition, this trial enrolled Japanese patients only and thus its generalizability to the Canadian CHC population may be limited. All but one study was uncontrolled and none of the trials compared DCV to another interferon-free DAA regimen; thus, it is difficult to determine DCV's place in therapy, relative to other DAAs currently in use in Canada.

3.6 Efficacy

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

3.6.1 Sustained Virologic Response

a) Daclatasvir plus Asunaprevir

In the DUAL study, the SVR12 rate was 90% (95% CI, 85% to 94%) in the treatment-naive genotype 1b CHC cohort who received DCV + ASV for 24 weeks. The lower bound of the 95% CI (85%) exceeded the 68% historical control rate for TEL + PR that was specified as the primary objective (Table 11), but no statistical testing was performed. SVR12 was achieved in 82% (95% CI, 77% to 87%) of those in the treatment-experienced and in the interferon-ineligible or -intolerant cohorts.

In the NIPPON study, 81% (95% CI, 72% to 89%) of the treatment-experienced genotype 1b CHC cohort and 88% (95% CI, 83% to 94%) of the interferon-ineligible or -intolerant cohort achieved SVR12 after 24 weeks of DCV + ASV therapy (Table 11).

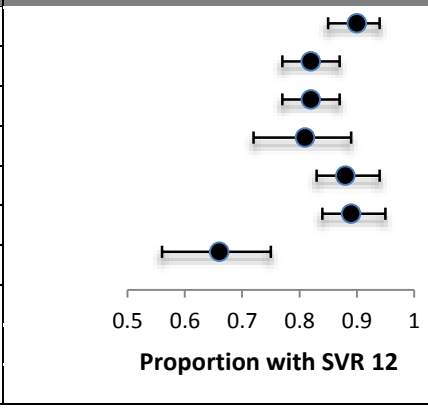
In Study 031, 89% of treatment-naive genotype 1b CHC patients randomized to DCV + ASV (mITT and PP) achieved SVR12 versus 66% (PP) or 62% (mITT) of those on TEL + PR (Table 11, Appendix 4 Table 15). DCV + ASV was deemed non-inferior to TEL + PR in terms of SVR12 as the lower bound of the 95% CI was greater than the –15% non-inferiority margin and also exceeded 0% in the mITT population (risk difference [RD] 26%; 95% CI, 16% to 36%). Non-inferiority was also met based on the PP population (RD 19%; 95% CI, 9% to 28%), which was reported as a sensitivity analysis.

Among patients with genotype 1b CHC treated with DCV + ASV in the DUAL, NIPPON, and 031 studies, SVR12 rates were similar in patients with and without cirrhosis, and in those with prior null or partial

response to PR therapy (Appendix 4, Table 14 and Table 15). In Study 031, treatment-naive patients with more severe fibrosis who received TEL + PR had a lower SVR12 rate than those with less severe fibrosis.

In the overall DUAL study population, the L31 HCV NS5A resistant variant was present in 5% of patients at baseline, of whom 41% achieved SVR12, and among the 8% of patients with the Y93 variant, 38% achieved SVR12.

TABLE 11: PROPORTION OF CHRONIC HEPATITIS C GENOTYPE 1B PATIENTS WHO ACHIEVED SVR12 (DUAL, NIPPON, 031)

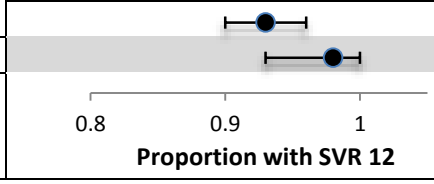
Study	Population	Treatment	% SVR12 (95% CI)	
DUAL	Naive	DCV + ASV 24 wks	90% (85 to 94%)	
	Experienced	DCV + ASV 24 wks	82% (77 to 87%)	
	Ineligible/intolerant	DCV + ASV 24 wks	82% (77 to 87%)	
NIPPON	Experienced	DCV + ASV 24 wks	81% (72 to 89%)	
	Ineligible/intolerant	DCV + ASV 24 wks	88% (83 to 94%)	
031	Naive	DCV + ASV 24 wks	89% (84 to 95%)[a]	
	Naive	TEL + PR 24 wks	66% (56 to 75%)[a]	

ASV = asunaprevir; CHC = chronic hepatitis C; CI = confidence interval; DCV = daclatasvir; PR = pegylated interferon plus ribavirin; SVR12 = sustained virologic response 12 weeks after the end of treatment; TEL = telaprevir; wks = weeks.
[a] Per-protocol analysis; all other data based on modified intention-to-treat analysis.

Daclatasvir and Asunaprevir Plus PR

Among treatment-experienced genotype 1 and 4 CHC patients who received DCV/ASV + PR for 24 weeks, 93% (95% CI, 90% to 96%) and 98% (95% CI, 93% to 100%) achieved SVR12, respectively, in the QUAD study (Table 12). SVR12 rates were similar among patients with and without cirrhosis and among patients with prior null or partial response to PR therapy (Appendix 4, Table 16). 87% of patients with genotype 1a and 99% of those with genotype 1b achieved SVR12.

TABLE 12: PROPORTION OF CHRONIC HEPATITIS C GENOTYPE 1 OR 4 PATIENTS WHO ACHIEVED SVR12 (QUAD STUDY)

Study	Population	Treatment	% SVR12 (95% CI)	
QUAD	G1 experienced	DCV/ASV + PR 24 wks	93% (90% to 96%)	
	G4 experienced	DCV/ASV + PR 24 wks	98% (93% to 100%)	

ASV = asunaprevir; CHC = chronic hepatitis C; CI = confidence interval; DCV = daclatasvir; G = genotype; PR = pegylated interferon plus ribavirin; SVR12 = sustained virologic response 12 weeks after the end of treatment; wks = weeks.

3.6.2 Relapse and On-Treatment Failure

a) Daclatasvir Plus Asunaprevir

In patients with genotype 1b CHC who received DCV + ASV for 24 weeks, the proportion of treatment-naive, treatment-experienced, or interferon-ineligible and/or intolerant patients who relapsed ranged from 3% to 9% (Appendix 4, Table 14 and Table 15). In Study 031, the relapse rate was lower among treatment-naive patients randomized to DCV + ASV than TEL + PR (8% versus 19%, respectively). One additional patient in the DCV + ASV group had a late relapse (after 12 weeks of follow-up) in Study 031 (total relapses 10/115, 9%). The proportion of patients with on-treatment failure to DCV + ASV ranged from 3% to 6% in treatment-naive patients, 13% to 14% in treatment-experienced patients, and 4% to 12% in interferon-ineligible or -intolerant cohorts. In Study 031, 3% of patients on DCV + ASV had an on-treatment failure compared with 23% of those on TEL + PR.

b) Daclatasvir and Asunaprevir Plus PR

Among treatment-experienced patients who received DCV/ASV + PR for 24 weeks, 2% of those with genotype 1 CHC and no patients with genotype 4 CHC relapsed (Appendix 4, Table 16). Four per cent of genotype 1 patients and no genotype 4 patients had an on-treatment failure.

3.6.3 Health-Related Quality of Life

Health-related quality-of-life data were measured using the SF-36 in Study 031 and QUAD. SF-36 data were collected in the DUAL study, but the results were not available.

a) Daclatasvir Plus Asunaprevir

In Study 031 (genotype 1b treatment-naive CHC), baseline scores for each SF-36 domain (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health) were similar in the DCV + ASV and TEL + PR groups (range DCV + ASV: 49.3 to 56.5; TEL + PR: 50.0 to 56.4) (Appendix 4, Table 17). At the end of treatment with DCV + ASV, mean domain scores changed from –2.1 to +1.5, whereas the TEL + PR group scores all decreased (range –10.5 to –4.3). Twelve weeks after the end of treatment, the domain scores were similar to baseline values in the DCV + ASV group (mean change from baseline to 12 weeks after therapy, range: –1.3 to +1.1) and in the TEL + PR group (range –2.9 to 1.3). In the TEL + PR group, the mean role emotional (–2.9) and role physical (–2.4) scores had decreased more than 2 points from baseline, 12 weeks after the end of treatment. In general use, the minimal clinically important difference (MCID) for each SF-36 domain is estimated to be 2 to 4 points. No statistical comparisons between groups were reported.

b) Daclatasvir and Asunaprevir Plus PR

In the QUAD study, baseline SF-36 domain scores ranged from 48.2 to 53.0 in the treatment-experienced genotype 1 and 4 CHC patients. Domain scores decreased 2.6 to 9.8 points from baseline at the end of treatment, and were similar to baseline, 12 weeks after the end of treatment (mean change from baseline to 12 weeks after therapy, range: –1.0 to +1.7) (Appendix 4, Table 17). No statistical analyses were reported.

3.7 Harms

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

3.7.1 Adverse Events

The proportion of patients who reported adverse events ranged from 80% to 89% while on DCV + ASV, and was 99% among those who received DCV/ASV + PR (Table 13). In the DUAL study, the incidence of adverse events over the first 12 weeks of therapy was similar between those randomized to placebo or DCV + ASV (73% versus 80%, respectively). In Study 031, 89% of patients on DCV + ASV, compared with 100% on TEL + PR, reported an adverse event.

3.7.2 Serious Adverse Events

Serious adverse events were reported by 3% to 7% of patients who received DCV + ASV and 6% of those who received DCV/ASV + PR (Table 13). In the first 12 weeks of the DUAL study, 1% and 3% of those on placebo or DCV + ASV, respectively, experienced a serious adverse event. In Study 031, 4% and 5% of patients in the DCV + ASV and TEL + PR groups, respectively, reported a serious adverse event.

3.7.3 Withdrawals Due to Adverse Events

Few patients treated with ASV discontinued therapy due to adverse events (DCV + ASV: 1% to 7%; DCV/ASV + PR: 5%) (Table 13). No patients on placebo discontinued therapy due to adverse events, compared with three patients (1%) in the first 12 weeks of the DUAL study. In Study 031, 20% of patients on TEL + PR stopped all therapy due to adverse events, compared with 5% of patients on DCV + ASV.

3.7.4 Mortality

One death occurred in the QUAD study, in a patient who received DCV/ASV + PR. No other deaths were reported in the included studies (Table 13).

3.7.5 Notable Harms

During the treatment period, the most frequently reported adverse events among patients who received ASV were headache (13% to 31%), nausea (4% to 17%), and fatigue (2% to 42%) (Table 13). The incidence of pegylated interferon- or ribavirin-related adverse events (e.g., anemia, rash, pruritus, neutropenia, fatigue, and depression) was higher in the DCV/ASV + PR and TEL + PR treatment groups, than in the interferon-free cohorts.

In Study 031, two harms-related secondary outcomes were reported. Rash-related events during the first 12 weeks of treatment that led to study drug discontinuation, or were classified as a serious adverse event or grade 3 or 4 adverse event, were reported in no patients on DCV + ASV and 15 (14%) patients on TEL + PR (RD –12.6%; 95% CI, –18.8% to –6.5% for DCV + ASV versus TEL + PR). Anemia, defined as a decline in hemoglobin to < 100 g/L during the first 12 weeks of treatment, was reported in no DCV + ASV-treated patients and 53 (48%) patients on telaprevir plus PR (RD –47.7%; 95% CI, –57.0% to –38.5%). Among the other trials, rash was reported in 5% to 11% of patients receiving DCV + ASV and 29% on DCV/ASV + PR. Anemia was reported by 0% to 3% of patients on DCV + ASV and 19% of those on DCV/ASV + PR.

TABLE 13: HARMS

	Hallmark DUAL Genotype 1b					Hallmark NIPPON Genotype 1b		Study 031 Genotype 1b		QUAD
	Randomized DB Baseline to Week 12 Treatment-Naive		DB/OL Baseline to End of Treatment Treatment-Naive	OL Baseline to End of Treatment DCV + ASV 24 Weeks		OL Treatment-Experienced	OL Ineligible/ Intolerant	Randomized OL Treatment-Naive IFN-Ineligible		Treatment-Experienced Genotype 1 and 4
	Placebo	DCV + ASV 24 weeks	DCV + ASV 24 weeks	Treatment-experienced	Ineligible / intolerant	DCV + ASV 24 weeks		DCV + ASV 24 weeks	TEL + PR	DCV/ASV + PR 24 weeks
N	102	205	205	205	235	87	135	119	111	398
Any AE	74 (73)	164 (80)	176 (86)	167 (81)	204 (87)	74 (85)	118 (87)	106 (89)	111 (100)	393 (99)
SAE	1 (1)	7 (3)	12 (6)	11 (5)	16 (7)	4 (5)	9 (7)	5 (4)	6 (5)	22 (6)
Death	0	0	0	0	0	0	0	0	0	1 (< 1%)
AE leading to discontinuation of all study drugs	0	3 (1)	6 (3)	2 (1)	2 (1)	2 (2)	9 (7)	6 (5)[a]	22 (20)[a]	18 (5)
Notable AE										
Anemia	2 (2)	1 (< 1)	2 (1)	3 (1)	7 (3)	2 (2)	3 (2)	0	93 (84)	77 (19)
Fatigue	18 (18)	35 (17)	43 (21)	45 (22)	52 (22)	2 (2)	8 (6)	12 (10)	25 (23)	165 (42)
Rash	5 (5)[b]	14 (7)[b]	16 (8)[b]	11 (5)[b]	19 (8)[b]	7 (8)[b]	12 (9)[b]	13 (11)[b]	89 (80)[b]	117 (29)[b]
Pruritus	8 (8)	7 (3)	8 (4)	14 (7)	18 (8)	7 (8)	2 (2)	8 (7)	30 (27)	104 (26)
Depression	1 (1)	5 (2)	8 (4)	3 (2)	9 (4)	0	1 (< 1)	0	3 (3)	34 (9)
Headache	17 (17)	42 (20)	50 (24)	50 (24)	59 (25)	17 (20)	18 (13)	17 (14)	49 (44)	124 (31)
Neutropenia	0	1 (1)	1 (< 1)	0	1 (< 1)	0	1 (< 1)	1 (< 1)	30 (27)	59 (15)
Nausea	12 (12)	23 (11)	25 (12)	22 (11)	28 (12)	6 (7)	6 (4)	14 (12)	64 (58)	66 (17)
Diarrhea	10 (10)	22 (11)	24 (12)	28 (14)	51 (22)	10 (12)	12 (9)	9 (8)	12 (11)	70 (18)
Asthenia	1 (1)	4 (2)	4 (2)	12 (6)	25 (11)	0	1 (<1)	NR	NR	96 (24)

AE = adverse event; ASV = asunaprevir; DB = double-blind; DCV = daclatasvir; IFN = interferon; N = number of patients; NR = not reported; OL = open-label; PR = pegylated interferon plus ribavirin; RBV = ribavirin; TEL = telaprevir.

[a] Six patients in the DCV + ASV arm and 69 (62%) patients in the TEL + PR arm had an adverse event that led to discontinuation of any study drug.

[b] Composite of rash-related *Medical Dictionary for Regulatory Activities* (MedDRA) terms.

Source: Manns,[14] Kumada,[15] Jensen,[16] Clinical Study Reports.[10-13]

4. DISCUSSION

4.1 Summary of Available Evidence

Four open-label studies met the inclusion criteria, including one RCT (Study 031) and three non-comparative studies (DUAL, NIPPON, QUAD). The patients enrolled had genotype 1b (DUAL, NIPPON, 031), or genotype 1 or 4 (QUAD), and included treatment-naive (DUAL, 031), treatment-experienced (DUAL, NIPPON, QUAD), and interferon-ineligible or -intolerant cohorts (DUAL, NIPPON).

DCV was combined with ASV in three trials (DUAL, NIPPON, 031), and with ASV and PR in one trial (QUAD). The primary outcome in all studies was SVR12 or SVR24. Study 031 assessed whether DCV + ASV was non-inferior to TEL + PR in terms of SVR12. The DUAL study compared the SVR12 rate in the treatment-naive population to a historical control rate for TEL + PR (68%).

Two trials were conducted in Japan (NIPPON, 031) and two were conducted in multiple countries in North and South America, Europe, and Asia (DUAL, QUAD). Key limitations included the lack of randomization and control groups. Limited data were available in patients with genotype 4 CHC.

4.2 Interpretation of Results

4.2.1 Efficacy

DCV+ ASV for 24 weeks achieved SVR12 rates between 81% and 90% among patients with genotype 1b CHC, and showed similar response rates regardless of the patients' prior treatment history, or presence of cirrhosis. In treatment-naive patients, the SVR12 rate for DCV + ASV (90%) exceeded the 68% historical control rate for TEL + PR in the DUAL study, and was non-inferior to TEL + PR (89% versus 66%, PP analysis) based on Study 031. Relapse rates ranged from 3% to 9% among genotype 1b patients that received DCV + ASV, and were lower than TEL + PR (19%). In the treatment-experienced genotype 1b patients who did not achieve SVR12 (DUAL, NIPPON), more patients had an on-treatment failure than a relapse.

SVR12 rates exceeded 90% in treatment-experienced patients with genotype 1 or 4 CHC (93% and 98%, respectively) who received DCV/ASV + PR for 24 weeks, and were similar across subgroups based on fibrosis severity, genotype subtype, and prior treatment response. The reported relapse and on-treatment failure rates were low (≤ 4%).

Additional data suggest that response rates in certain subpopulations of interest, such as patients who relapse on an interferon-based regimen other than TEL, and patients coinfected with HIV on antiretroviral therapy, achieve similar SVR12 response rates to those observed in the trials included in this review (95.5% and 96%, respectively). These data have been summarized in APPENDIX 6 and APPENDIX 7, respectively, as the trials were not randomized, nor considered pivotal, and were therefore not included in the primary review.

Although the manufacturer is seeking Health Canada approval for DCV/ASV + PR in patients with genotype 4 CHC, the available data are limited by the small sample size (N = 44) enrolled in the QUAD study (genotype 4 cohort). No clinical trial data were available for the DCV/ASV + PR regimen in treatment-naive patients with genotype 1 or 4 CHC: Health Canada has extrapolated data from other populations to support these recommended dosing regimens.[23] Moreover, the number of patients with cirrhosis enrolled in some trials was limited.

Quality-of-life data were reported as exploratory outcomes in three studies. These data showed no clinically important changes in quality-of-life scores at the end of treatment, or 12 weeks after treatment, in patients who received DCV + ASV. Among patients who received an interferon-based regimen (TEL + plus PR or DCV/ASV + PR), quality-of-life scores decreased substantially on treatment, but returned to baseline values 12 weeks after the end of treatment. The lack of a clinically important change in quality-of-life data is consistent with other interferon-free regimens. The reduction in quality-of-life scores in interferon treatment arms is also consistent with other trial data assessing interferon-based regimens in this population.[33-35]

No data were available for the other clinical outcomes of interest described in the protocol.

The uncontrolled studies provide limited data that may be used to estimate the comparative effectiveness of DCV. Although Study 031 used TEL + PR as a comparator, TEL is no longer marketed in Canada and this trial enrolled a Japanese population, which may limit its generalizability. The manufacturer provided an indirect treatment comparison, which found that in patients with genotype 1b CHC, DCV + ASV was statistically significantly more effective in achieving SVR than TEL or BOC + PR, and, in some subpopulations, was superior to SIM or SOF + PR. Specifically, DCV + ASV was statistically significant versus SIM + PR in treatment-naive genotype 1b patients (based on the network meta-analysis), and in treatment-experienced genotype 1b patients (based on the matching-adjusted indirect comparison [MAIC]) (APPENDIX 8). The MAIC methods used in the manufacturer's analyses have limited ability to control confounding; thus, these findings need to be interpreted with caution. Moreover, the manufacturer's analysis did not include the interferon-free DAA regimens, which limits the utility of the indirect comparison. CADTH conducted an indirect treatment comparison that evaluated the efficacy and safety of PR-based and interferon-free DAA regimens for CHC.[9] In treatment-naive genotype 1b CHC patients, the rate of SVR12 was statistically significantly lower for DCV +ASV compared with LDV/SOF (RD –7%) and was not statistically significantly different from SOF + RBV or ombitasvir/paritaprevir/ritonavir + dasabuvir.[9] In treatment-experienced genotype 1b patients, SVR12 was statistically significantly lower for DCV + ASV than ombitasvir/paritaprevir/ritonavir + dasabuvir (RD –18%) and not significantly different compared with LDV/SOF.[9] Among treatment-experienced genotype 1 CHC patients, no statistically significant differences in SVR12 were detected between DCV/ASV + PR and other interferon-free DAA regimens (DCV + ASV, SIM + SOF, LDV/SOF or ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin).[9] In non-cirrhotic treatment-experienced patients with genotype 4 CHC, no statistically significant differences in SVR12 were detected between DCV/ASV + PR compared with ombitasvir/paritaprevir/ritonavir + ribavirin; however, the number of trials in this analysis were limited.[9] The recommendation from CDEC on the CADTH Therapeutic Review *Drugs for Chronic Hepatitis C Infection* was the use of LDV/SOF and ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin as preferred regimens for treatment-naive and PR-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status; and SOF + PR for 12 weeks in treatment-naive patients with CHC genotype 4 infection who are non-cirrhotic.[22] However, CDEC acknowledged the difficulty in assessing comparative efficacy, safety, and cost-effectiveness, given the lack of appropriately controlled trials. Methods for synthesizing evidence from single-arm trials in indirect treatment comparisons are emerging, and analyses employing these methods are associated with greater uncertainty compared with indirect treatment comparisons based on controlled trials.[22] Asunaprevir was not commercially available at the time of the publication of the CADTH Therapeutic Review and, thus, no recommendations were made with regard to this drug.

4.2.2 Harms

In the four trials, the incidence of adverse events was high (> 73%) for all treatment groups, with headache, nausea, diarrhea, and fatigue reported most frequently. Of the trials, only two provided comparative adverse event data (DUAL, 031). In the DUAL study, the incidence of any adverse event and of notable adverse events was similar for DCV + ASV and placebo during the initial 12-week double-blind treatment period. TEL + PR was associated with statistically significantly higher incidence of anemia and clinically significant rash compared with DCV + ASV, in Japanese CHC patients. Patients who received DCV/ASV + PR also reported a higher frequency of rash, anemia, and pruritus, which was consistent with the adverse event profile of interferon-based therapies. The incidence of serious adverse events was ≤ 7% in all treatment groups, including those who received PR.

The proportion of patients who stopped treatment due to adverse events was similar among patients who received DCV + ASV or DCV/ASV + PR, and was higher among those administered TEL + PR than those on DCV + ASV in Study 031. The manufacturer-provided indirect treatment comparison indicated that in patients with genotype 1b CHC, DCV + ASV had statistically significantly lower rates of discontinuation due to adverse events, than PR alone or PR in combination with TEL or BOC, in treatment-naive patients only. There was no significant difference in discontinuation due to adverse events in treatment-experienced patients with genotype 1b CHC. In trials that assessed LDV/SOF and ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavirin, withdrawal rates reported (0% to 1.1% and 0% to 1.8%, respectively) were similar to or lower than those reported in some DCV + ASV arms.[33,34] However, without a formal comparison, no conclusion can be made based on these observed differences, and multiple factors could contribute to these differences other than drug therapy in open-label trials. It should be noted that higher percentages can be reported in these DCV trials, while absolute numbers are small, due to the small number of patients enrolled in some arms, making it difficult to draw conclusions on the true occurrence of adverse effects in some subpopulations. The CADTH indirect treatment comparison found that DCV + ASV was associated with statistically significantly less rash than ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin, and higher depression than LDV/SOF in treatment-naive CHC patients, but was not significantly different from other interferon-free DAA regimens in treatment-naive and experienced patients.[9] Overall, DCV + ASV regimens were associated with less rash and anemia than PR-based treatments.[9] DCV/ASV + PR was associated with a significantly higher risk of rash than interferon-free DAA regimens (except SIM + SOF) and higher risk of anemia than LDV/SOF or ombitasvir/paritaprevir/ritonavir + dasabuvir, in treatment-experienced CHC patients.[9] Of note, the relatively small size and uncontrolled nature of the available studies for DAA-based regimens did not allow for a thorough assessment of harms in the CADTH Therapeutic Review.

Except for the first 12 weeks in the DUAL study, these trials were open-label, and so reporting of adverse events may potentially be biased by knowledge of the treatment received. This should be considered when interpreting the adverse event data, particularly for Study 031.

5. CONCLUSIONS

Based on data from three uncontrolled studies and one RCT, ASV was associated with high rates of SVR12 when combined with DCV in patients with genotype 1b CHC, and combined with DCV plus PR in patients with genotype 1or 4 CHC infection. DCV + ASV was non-inferior to TEL + PR, based on one RCT in Japanese treatment-naive patients with genotype 1b CHC.

DCV + ASV combination therapy appears to be better tolerated than TEL + PR or DCV/ASV + PR, and was not associated with clinically important decreases in quality of life during treatment. However, the health-related quality of life data were exploratory.

The data were limited for some populations, specifically patients with genotype 4 CHC and patients with cirrhosis, due to the small numbers of patients treated.

No direct evidence was available on the comparative efficacy and safety of ASV combined with DCV or DCV plus PR versus other DAA regimens or combinations currently in use in Canada. The CADTH Therapeutic Review provides some indirect evidence for ASV-based regimens; however, it must be interpreted considering the uncertainty associated with methods for synthesizing evidence from single-arm trials.

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
Four patient groups submitted input.

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

Canadian Treatment Action Council (CTAC) is a national nongovernmental organization whose mandate is to address access to treatment, care, and support for people living with HIV or hepatitis C virus (HCV). Full membership is limited to persons living with HIV/AIDS or organizations with a substantial HIV/AIDS mandate. CTAC has received unrestricted educational grants from pharmaceutical companies other than Bristol-Myers Squibb. CTAC made no statement with regard to possible conflicts of interest in the preparation of this submission.

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

Hepatitis C Education and Prevention Society (HepCBC) is a non-profit organization run by and for people affected by HCV in British Columbia. HepCBC focuses on providing peer support groups, anti-stigma activities, prevention education, general hepatitis information, and encouraging testing among at-risk groups. HepCBC received funding from pharmaceutical companies including Bristol-Myers Squibb to support its educational activities. Three of those who contributed individual patient submissions have received funding from pharmaceutical companies to attend conferences.

2. Condition and Current Therapy-Related Information
The information for this section was gathered through interviews with patients affected by hepatitis C, physicians who treated patients with asunaprevir, and online surveys.

HCV is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, cancer, liver failure, and even death. For those coinfected with HIV, liver disease progression may be exacerbated. Some patients have few or no symptoms, but others experience fatigue, abdominal pain, muscle or joint pain, itchiness, digestive problems, depression, insomnia, nausea, loss of appetite, headaches, disrupted sleep, slower motor reflexes, psoriasis, and diarrhea. In some patients, the disease affects their cognitive functions, in that their concentration and/or attention span, speed of thought, fluency of speech, learning, and memory are affected. 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.

Patients must cope with the stigma associated with HCV and are often reluctant to disclose their HCV status for fear of rejection, discrimination, or ostracism. The social stigma, fear of spreading the infection, and the uncertainty regarding their future health exact a high emotional toll on patients that may lead to depression, anxiety, loss of hope, and social isolation. Often marriages and other personal relationships cannot survive the strain. To patients, a cure means a return to normal life, the ability to work full time, think clearly, and have intimate contact with others. No more worries about dying decades too soon.

Spouses and loved ones who care for patients with HCV are faced with a substantial burden, as the symptoms of HCV and side effects of interferon-based therapies 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 ones' mood swings, dietary problems, and lack of energy and concentration, while shouldering the responsibility for managing doctors' 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.

The current standard of care is changing. Formerly, it was pegylated interferon with ribavirin alone or with either telaprevir or boceprevir, or more recently, simeprevir, or sofosbuvir (for HCV genotype 1). Adverse effects can be severe and debilitating, such as extreme fatigue, anemia, depression, anxiety, mood swings, rashes, headaches, chills, nausea, weight loss, suppressed appetite, hair loss, and joint pain. In addition, some triple-therapy regimens require patients to take up to 20 pills throughout the day, with specific food requirements. Patients have no way of knowing whether the treatments will be successful and if their efforts to complete therapy and endure the side effects will be worth it. Adverse effects of treatment may affect patients' ability to continue working and to manage their household or childcare. Many patients have contraindications or cannot tolerate interferon and thus are ineligible for interferon-based regimens. Injections associated with interferon can be a triggering factor and a source of anxiety for those with a history of injection drug use. Those who have failed interferon-based treatments have few treatment options. One patient group indicated that a large percentage of patients they come into contact with were being "warehoused," either by doctors or by themselves, simply rejecting the idea of taking current therapies, knowing vastly superior drugs are so close to being approved.

3. Related Information About the Drug Being Reviewed

The expectations for asunaprevir is that the treatment's high sustained virologic responses (SVRs), which have been reached in clinical trials, when asunaprevir is combined with other drugs, will translate into a better chance of a cure for patients and, thus, enable them to start their lives anew. Due to its low toxicity and lack of drug interactions, asunaprevir is expected to open up treatment to patients who had contraindications to, or who couldn't tolerate, interferon-based treatments, such as those with HIV coinfection or autoimmune conditions. With a cure, they expect that their cirrhosis will reverse, and their risk of end-stage liver disease will be reduced. Some may be able to return to work, and the quality of life of everyone will improve.

Patients tend not to differentiate the various new drugs from one another because they are all so much better than the existing ones, and share the characteristics of being mostly tested on genotype 1, far greater efficacy, a far shorter treatment time, no interferon or needles, very few side effects, and an extremely high price tag. They are excited about asunaprevir's diverse uses, and that it has been studied in combination with other new treatments and in patients with cirrhosis. However, some patients were concerned about side effects — specifically that ribavirin might be needed for some HCV sufferers. Several patients noted that they were discouraged from seeking treatment because of the continued presence of ribavirin in contemporary therapy options. Patients also questioned the place of asunaprevir amid contemporary HCV therapies like sofosbuvir and ledipasvir/sofosbuvir (treatments including sofosbuvir, with which daclatasvir is often paired) and suggested it might be designed for more difficult-to-treat populations. While most patients are willing to accept serious adverse effects for weeks if there is a high probability of a cure, the expectation is that asunaprevir has far fewer adverse side effects than past treatments.

Physicians treating patients with daclatasvir plus asunaprevir found that their patients had a fairly easy time with treatment, with no noticeable side effects, and some patients found that their quality of life improved significantly. Patients felt better on the medications than they did prior to starting therapy and several patients actually went back to work and off disability while they were on these new drugs. A patient with cirrhosis who received daclatasvir plus asunaprevir indicated that after being cured, she could live a relatively normal life again. The treatment had no side effects and she was able to walk a half-marathon in the middle of treatment. One year after treatment, the cirrhosis was almost gone. Another patient had a Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) score of F2 before treatment, and one year later her METAVIR score was F1. She indicated that it was great not to have to use a needle to inject medications, and amazingly, the treatment had no side effects. She said she is slowly and steadily improving and has her energy back. She is able to travel and volunteer, and is not in constant fear of infecting anyone.

4. Additional Information

Patients are concerned that the prices of these drugs will be so high that CADTH (and/or provincial Pharmacare plans) will either not approve the treatment at all, or make the overage criteria require patients to undergo and fail very challenging standard treatments (with both interferon and ribavirin) before they have access to asunaprevir. Delaying treatment until liver disease is more advanced affects patients' physical and mental well-being. It is frustrating for individuals, especially those who are experiencing multiple barriers, to be told that they are not sick enough to qualify for treatment. Patients worry about the liver damage that may be caused by delaying treatment. The sooner a person is effectively treated (i.e., cured), the less chance they have of inadvertently infecting someone else. Improved treatments for hepatitis C have the potential to reduce social system and health care costs for patients with severe liver disease. Delays in the funding decision process will mean that some patients' time will run out. One patient indicated that there are no other diseases in which a patient has to prove significant damage to his/her bodily organs in order to get treated. And there are no others in which a patient has to take such clearly inferior — even harmful — treatments simply because of price. Thus, there are concerns that this treatment will not be accessible because it is either not covered by public drug plans or the criteria for coverage will limit access.

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:	March 18, 2016
Alerts:	Monthly search updates June 15, 2016 (date of CDEC meeting)
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
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Asunaprevir* or Sunvepra* or BMS 650032 or BMS650032 or UNII-S9X0KRJ00S or 630420-16-5 or 63042016-5 or 630420-165 or "630420165").ti,ab,ot,kw,kf,hw,rn,nm.
2	1 use pmez
3	*asunaprevir/ or (Asunaprevir* or Sunvepra* or BMS 650032 or BMS650032 or UNII-S9X0KRJ00S or 630420-16-5).ti,ab.
4	3 use oemezd
5	2 or 4
6	5 not conference abstract.pt.
7	remove duplicates from 6

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:	March 2015, update April 2016
Keywords:	Sunvepra (asunaprevir)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Kinugasa H, Ikeda F, Takaguchi K, Mori C, Matsubara T, Shiraha H, et al. Low frequency of drug-resistant virus did not affect the therapeutic efficacy in daclatasvir plus asunaprevir therapy in patients with chronic HCV genotype-1 infection. Antivir Ther. 2016;21(1):37-44.	Not an RCT
Sugimoto K, Kim SR, Kim SK, Imoto S, Tohyama M, Kim KI, et al. Comparison of Daclatasvir and Asunaprevir for Chronic HCV 1b Infection with Telaprevir and Simeprevir plus Peginterferon and Ribavirin, with a Focus on the Prevention of Occurrence and Recurrence of Hepatocellular Carcinoma. Oncology. 2015;89 Suppl 2:42-6.	Not an RCT
Toyoda H, Kumada T, Tada T, Takaguchi K, Ishikawa T, Tsuji K, et al. Safety and efficacy of dual direct-acting antiviral therapy (daclatasvir and asunaprevir) for chronic hepatitis C virus genotype 1 infection in patients on hemodialysis. J Gastroenterol. 2016 Feb 12.	Not an RCT
Uchida Y, Kouyama JI, Naiki K, Sugawarav K, Inao M, Imai Y, et al. Development of rare RAVs that are extremely tolerant against NS5A inhibitors during daclatasvir/asunaprevir therapy Via a Two-Hit mechanism. Hepatol Res. 2016 Feb 15.	Not an RCT
Yoshimi S, Imamura M, Murakami E, Hiraga N, Tsuge M, Kawakami Y, et al. Long term persistence of NS5A inhibitor-resistant hepatitis C virus in patients who failed daclatasvir and asunaprevir therapy. J Med Virol. 2015 Nov;87(11):1913-20.	Not an RCT
Suda G, Kudo M, Nagasaka A, Furuya K, Yamamoto Y, Kobayashi T, et al. Efficacy and safety of daclatasvir and asunaprevir combination therapy in chronic hemodialysis patients with chronic hepatitis C. J Gastroenterol. 2016 Jan 14.	Not an RCT
Piroth L, Paniez H, Taburet AM, Vincent C, Rosenthal E, Lacombe K, et al. High Cure Rate With 24 Weeks of Daclatasvir-Based Quadruple Therapy in Treatment-Experienced, Null-Responder Patients With HIV/Hepatitis C Virus Genotype 1/4 Coinfection: The ANRS HC30 QUADRIH Study. Clin Infect Dis. 2015 Sep 1;61(5):817-25.	Phase 2 study
Bronowicki JP, Ratziu V, Gadano A, Thuluvath PJ, Bessone F, Martorell CT, et al. Randomized trial of asunaprevir plus peginterferon alfa and ribavirin for previously untreated genotype 1 or 4 chronic hepatitis C. J Hepatol. 2014 Dec;61(6):1220-7.	Wrong intervention; phase 2 study
Lok AS, Gardiner DF, Hezode C, Lawitz EJ, Bourliere M, Everson GT, et al. Randomized trial of daclatasvir and asunaprevir with or without PegIFN/RBV for hepatitis C virus genotype 1 null responders. J Hepatol. 2014 Mar;60(3):490-9.	phase 2 study
Everson GT, Sims KD, Rodriguez-Torres M, Hezode C, Lawitz E, Bourliere M, et al. Efficacy of an interferon- and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 in treatment-naive patients with HCV genotype 1 infection. Gastroenterology. 2014 Feb;146(2):420-9.	Wrong intervention; phase 2 study
Suzuki Y, Ikeda K, Suzuki F, Toyota J, Karino Y, Chayama K, et al. Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infection and limited treatment options. J Hepatol. 2013 Apr;58(4):655-62.	Phase 2 study
Chayama K, Takahashi S, Toyota J, Karino Y, Ikeda K, Ishikawa H, et al. Dual therapy with the nonstructural protein 5A inhibitor, daclatasvir, and the nonstructural protein 3 protease inhibitor, asunaprevir, in hepatitis C virus genotype 1b-infected null responders. Hepatology. 2012 Mar;55(3):742-8.	Phase 2 study

RCT = randomized controlled trial.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 14: EFFICACY OUTCOMES FOR DACLATASVIR + ASUNAPREVIR IN GENOTYPE 1b CHRONIC HEPATITIS C PATIENTS (STUDY DUAL, NIPPON)

Outcome	Hallmark DUAL Genotype 1b DCV + ASV 24 weeks						Hallmark NIPPON Genotype 1b DCV + ASV 24 weeks			
	Treatment-naive		Treatment-experienced (partial or null response to PR)		Ineligible and/or intolerant to PR[a]		Treatment-experienced (partial or null response to PR or IFN-beta/RBV)		Ineligible and/or intolerant to IFN-based therapy[b]	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
SVR12	182/203[c]	90% (85 to 94)[c]	168/205[c]	82% (77 to 87)[c]	192/235[c]	82% (77 to 87)[c]	70/87	81% (72 to 89)	119/135	88% (83 to 94)
SVR24	NR		NR		NR		70/87	81% (72, 89)	118/135	87% (82, 93)
SVR12 by fibrosis severity[d]										
No cirrhosis	153/171	89%	113/142	80%	104/124	84%	10/11	91%	10/11	91%
Cirrhosis	29/32	91%	55/63	87%	88/111	79%	60/76	79%	108/124	87%
SVR12 by prior treatment response [d]										
Null	NA		98/119	82%	NA		39/48	81%	NA	
Partial response	NA		68/84	81%	NA		28/36	78%	NA	
Undetermined	NR		NR		NA		3/3	100%	NA	
On-treatment failure[e]	13/203	6%	29/205	14%	29/235	12%	11/87	13%	6/135	4%
Relapse	5/189	3%	7/174	4%	12/204	6%	6/76	8%	11/129	9%

ASV = asunaprevir; CI = confidence interval; DCV = daclatasvir; HCV = hepatitis C virus; IFN = interferon; N = number of patients; NA = not applicable; NR = not reported; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RNA = ribonucleic acid; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment.

[a] Ineligible or intolerant (or both) patients included those with depression, anemia or neutropenia, or compensated advanced fibrosis or cirrhosis (F3/F4) with thrombocytopenia (treatment-naive or treatment-experienced).

[b] Patients ineligible for interferon-based therapy were treatment-naive and considered poor candidates for IFN-based therapy because of medical complications including anemia, neutropenia, thrombocytopenia, depression, advanced age (≥ 65 years), or other conditions deemed not suitable for IFN-based therapy by the investigator, including hypertension, diabetes mellitus, autoimmune disease, and abnormal thyroid function. Patients intolerant to IFN-based therapy had received IFN-based therapy for less than 12 weeks and previously discontinued from therapy due to toxicities associated with interferon or ribavirin.

[c] Two additional patients in the treatment-naive, two patients in the ineligible or intolerant, and one patient in the treatment-experienced cohort with missing HCV RNA data 12 weeks after treatment achieved SVR based on data from the next available assessment (proportion with SVR12 in treatment-naive: 91%, 95% CI, 87 to 95%; treatment-experienced: 82%, 95% CI, 77 to 88%; ineligible and/or intolerant: 83%, 95% CI, 78 to 87%).

[d] Data reported for NIPPON study is SVR24.

[e] Patients with viral breakthrough, missing, or detectable HCV RNA at the end of treatment, or those who met futility criteria for stopping therapy.

Source: Manns,[14] Kumada.[15]

TABLE 15: EFFICACY OUTCOMES FOR DACLATASVIR + ASUNAPREVIR VERSUS TELAPREVIR PLUS PR IN GENOTYPE 1b CHRONIC HEPATITIS C PATIENTS (STUDY 031)

Outcome/Subgroup	Study 031 Genotype 1b Treatment-Naive				
	DCV + ASV 24 weeks		TEL + PR		DCV + ASV vs. TEL + PR
	n/N	% (95% CI)	n/N	% (95% CI)	RD (95% CI)
SVR12 — mITT	106/119	89% (84 to 95)	69/111	62% (53 to 71)	26% (16 to 36)
SVR12 — PP	106/119	89% (84 to 95)	65/99	66% (56, 75)	19% (9 to 28)
SVR24	NR	NR	NR	NR	NR
SVR12 by fibrosis severity[a]					NR
METAVIR F0	40/47	85%	25/32	78%	
METAVIR F1	22/25	88%	12/20	60%	
METAVIR F2	16/17	94%	11/18	61%	
METAVIR F3	13/15	87%	12/22	55%	
METAVIR F4	6/6	100%	4/13	31%	
Fibrosis severity not reported	9/9	100%	5/6	83%	
On-treatment failure[b]	4/119	3%	26/111	23%	NR
Relapse	9/115[c]	8%[c]	16/85	19%	NR

ASV = asunaprevir; DCV = daclatasvir; HCV = hepatitis C virus; METAVIR = Meta-analysis of Histological Data in Viral Hepatitis; mITT = modified intention-to-treat; N = number of patients; NA = not applicable; NR = not reported; PP = per-protocol; PR = pegylated interferon plus ribavirin; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; vs. = versus.

[a] Assessed using FibroTest.

[b] Patients with viral breakthrough, detectable HCV RNA at the end of treatment, or who met futility criteria for stopping therapy.

[c] One additional patient in DCV + ASV group had a late relapse after achieving SVR12.

Source: Clinical Study Report.[13]

TABLE 16: EFFICACY OUTCOMES FOR DACLATASVIR + ASUNAPREVIR PLUS PR IN GENOTYPE 1 & 4 CHRONIC HEPATITIS C PATIENTS (STUDY QUAD)

Outcome/Subgroup	Hallmark QUAD			
	DCV/ASV + PR 24 weeks			
	Genotype 1 Treatment-experienced		Genotype 4 Treatment-experienced	
	n/N	% (95% CI)	n/N	% (95% CI)
SVR12	329/354[a,b]	93% (90 to 96)	43/44[a]	98% (93 to 100)
SVR24	313/354[c]	88% (85 to 92)	42/44	96% (89 to 100)
SVR12 by fibrosis severity				
No cirrhosis	263/281	94%	24/24	100%
Cirrhosis	66/73	90%	19/20	95%
SVR12 by HCV subtype				
Genotype 1a	153/176	87%	NA	
Genotype 1b	176/178	99%	NA	
SVR12 by prior treatment response				
Partial response	110/120	92%	10/10	100%
Null response	219/234	94%	33/34	97%
On-treatment failure[d]	13/354[e]	4%[e]	0	0%
Relapse (during first 12 weeks post-treatment)	8/337	2%	0/43	0%

ASV = asunaprevir; DCV = daclatasvir; HCV = hepatitis C virus; LLOQ = lower limit of quantification; N = number of patients; NA = not applicable; NR = not reported; PR = pegylated interferon plus ribavirin; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment.

[a] Four patients with genotype 1 and one patient with genotype 4 CHC had missing HCV RNA data at 12 weeks post-treatment and were deemed failures. Of these, one genotype 1 and one genotype 4 patient achieved SVR24.

[b] One patient with genotype 4 was incorrectly assigned to the genotype 1a cohort and this patient achieved SVR12 and SVR24.

[c] Among the patients with no SVR24, 4 had a late relapse and 13 were missing data at the 24-week assessment.

[d] Patients with detectable HCV RNA at the end of treatment or viral breakthrough.

[e] Includes 2 patients who had < LLOQ detectable HCV RNA at the end of treatment, one of which achieved SVR24 (missing data for SVR12 assessment).

Source: Jensen,[16] Clinical Study Report.[12]

TABLE 17: SF-36 RESULTS FOR DACLATASVIR + ASUNAPREVIR ± PR IN GENOTYPE 1 & 4 CHRONIC HEPATITIS C PATIENTS (031, QUAD)

Outcome/Subgroup	Study 031 Genotype 1b		QUAD Genotype 1 & 4
	Treatment-naive	**Treatment-naive**	**Treatment-experienced**
	DCV + ASV 24 weeks	**TEL + PR**	**DCV/ASV + PR 24 weeks**
Physical Functioning			
Baseline, mean (SD)	54.2 (4.6), n = 119	54.8 (3.3), n = 111	51.1 (8.1), n = 392
End of treatment, mean (SD)	54.4 (4.6), n = 119	47.8 (8.5), n = 106	44.3 (9.8), n = 362[a]
Change from baseline to end of treatment, mean (SE)	0.18 (0.46), n = 119	–7.18 (0.77), n = 106	–6.82 (0.47), n = 358[a]
12 weeks post-treatment, mean (SD)	54.5 (4.8), n = 117	53.9 (4.3), n = 95	50.9 (7.9), n = 369
Change from baseline to 12 weeks post-treatment, mean (SE)	0.25 (0.51), n = 117	–1.03 (0.34), n = 95	–0.20 (0.36), n = 365
Role Physical			
Baseline, mean (SD)	53.4 (6.8), n = 119	54.7 (4.9), n = 111	48.6 (9.6), n = 394
End of treatment, mean (SD)	51.5 (7.3), n = 119	44.2 (10.6), n = 106	40.5 (10.5), n = 365[a]
Change from baseline to end of treatment, mean (SE)	–1.81 (0.74), n = 119	–10.47 (1.10), n = 106	–8.20 (0.54), n = 363[a]
12 weeks post-treatment, mean (SD)	52.2 (6.8), n = 117	52.1 (6.4), n = 95	48.2 (9.2), n = 372
Change from baseline to 12 weeks post-treatment, mean (SE)	–1.09 (0.65), n = 117	–2.39 (0.78), n = 95	–0.59 (0.43), n = 370
Bodily Pain			
Baseline, mean (SD)	54.2 (9.2), n = 117	56.5 (7.1), n = 111	53.0 (9.7), n = 390
End of treatment, mean (SD)	53.5 (9.3), n = 119	50.6 (9.5), n = 104	46.4 (10.3), n = 352[a]
Change from baseline to end of treatment, mean (SE)	–0.42 (0.87), n = 117	–5.91 (1.08), n = 104	–6.76 (0.57), n = 347[a]
12 weeks post-treatment, mean (SD)	54.3 (8.4), n = 117	56.3 (7.0), n = 95	52.2 (10.0), n = 374
Change from baseline to 12 weeks post-treatment, mean (SE)	0.37 (0.93), n = 115	0.13 (0.89), n = 95	–0.65 (0.50), n = 368
General Health			
Baseline, mean (SD)	49.3 (8.5), n = 119	50.0 (6.8), n = 111	48.8 (9.5), n = 392
End of treatment, mean (SD)	49.7 (8.4), n = 119	45.7 (8.7), n = 106	46.5 (10.4), n = 360[a]
Change from baseline to end of treatment, mean (SE)	0.38 (0.64), n = 119	–4.32 (0.87), n = 106	–2.59 (0.45), n = 357[a]
12 weeks post-treatment, mean (SD)	50.0 (8.4), n = 117	50.0 (8.2), n = 95	50.6 (9.7), n = 372
Change from baseline to 12 weeks post-treatment, mean (SE)	0.78 (0.61), n = 117	–0.36 (0.74), n = 95	1.66 (0.41), n = 369
Vitality			
Baseline, mean (SD)	56.5 (9.1), n = 119	56.4 (7.7), n = 111	53.0 (10.7), n = 388

Outcome/Subgroup	Study 031 Genotype 1b		QUAD Genotype 1 & 4
	Treatment-naive	**Treatment-naive**	**Treatment-experienced**
	DCV + ASV 24 weeks	**TEL + PR**	**DCV/ASV + PR 24 weeks**
End of treatment, mean (SD)	54.4 (9.7), n = 119	45.8 (12.3), n = 106	43.6 (11.6), n = 363[a]
Change from baseline to end of treatment, mean (SE)	–2.05 (0.73), n = 119	–10.34 (1.13), n = 106	–9.83 (0.60), n = 356[a]
12 weeks post-treatment, mean (SD)	55.4 (9.4), n = 117	55.4 (8.7), n = 95	54.1 (10.2), n = 374
Change from baseline to 12 weeks post-treatment, mean (SE)	–0.99 (0.67), n = 117	–0.28 (0.86), n = 95	0.84 (0.47), n = 366
Social Functioning			
Baseline, mean (SD)	53.0 (6.3), n = 119	54.0 (5.6), n = 111	50.2 (9.2), n = 390
End of treatment, mean (SD)	52.2 (7.6), n = 119	44.4 (11.7), n = 106	41.1 (11.3), n = 362[a]
Change from baseline to end of treatment, mean (SE)	–0.76 (0.65), n = 119	–9.55 (1.15), n = 106	–9.27 (0.59), n = 356[a]
12 weeks post-treatment, mean (SD)	52.6 (7.1), n = 117	51.9 (6.9), n = 95	49.3 (9.4), n = 374
Change from baseline to 12 weeks post-treatment, mean (SE)	–0.30 (0.66), n = 117	–1.95 (0.71), n = 95	–1.02 (0.45), n = 368
Role Emotional			
Baseline, mean (SD)	51.9 (7.2), n = 119	53.4 (5.2), n = 111	48.2 (10.3), n = 393
End of treatment, mean (SD)	50.1 (8.7), n = 119	42.8 (11.7), n = 106	39.9 (11.8), n = 365[a]
Change from baseline to end of treatment, mean (SE)	–1.81 (0.86), n = 119	–10.48 (1.14), n = 106	–8.33 (0.63), n = 362[a]
12 weeks post-treatment, mean (SD)	50.5 (7.5), n = 117	50.2 (7.9), n = 95	47.3 (10.0), n = 373
Change from baseline to 12 weeks post-treatment, mean (SE)	–1.25 (0.75), n = 117	–2.93 (0.85), n = 95	–1.03 (0.50), n = 370
Mental Health			
Baseline, mean (SD)	50.4 (9.3), n = 119	50.9 (8.3), n = 111	50.6 (9.6), n = 390
End of treatment, mean (SD)	52.0 (9.1), n = 119	45.2 (11.1), n = 106	44.0 (11.1), n = 364[a]
Change from baseline to end of treatment, mean (SE)	1.52 (0.73), n = 119	–5.50 (1.03), n = 106	–6.92 (0.54), n = 358[a]
12 weeks post-treatment, mean (SD)	51.3 (9.1), n = 117	51.6 (9.2), n = 95	50.0 (10.3), n = 373
Change from baseline to 12 weeks post-treatment, mean (SE)	1.05 (0.82), n = 117	1.27 (0.88), n = 95	–0.83 (0.48), n = 367

ASV = asunaprevir; DCV = daclatasvir; PR = pegylated interferon plus ribavirin; SD = standard deviation; SE = standard error; SF=36 = Short-Form (36) Health Survey; TEL = telaprevir.

[a] Week 24 visit.

Source: Clinical Study Reports.[12,13]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To review the validity of sustained virologic response at 12 weeks (SVR12) as a surrogate for SVR at 24 weeks (SVR24) and to summarize the characteristics of the Short-Form (36) Health Survey (SF-36) patient-reported outcome instruments.

Findings

TABLE 18: CHARACTERISTICS OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	Minimal Clinically Important Difference	References
SVR12 and 24	SVR at week 12 and 24 are end points for assessing response to drugs that treat chronic hepatitis C infection.	Yes	Not applicable	Chen et al.[36]
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 health-related quality of life.	Yes	2 to 4	Ware et al.[37]

SF-36 = Short-Form (36) Health Survey; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment.

Sustained Virologic Response

SVR24 is the standard primary end point for assessing response to drugs that treat chronic hepatitis C (CHC) infection.[36] However, SVR12 is an emerging outcome of interest, potentially providing a means for determining treatment response earlier in either RCTs or the clinic. In 2013, the FDA published a paper that sought to determine the predictive value of SVR12 as a surrogate for SVR24.[36] The authors reviewed data submitted to the FDA from 2002 to 2011 from 15 phase 2 and 3 studies that included various treatment durations of pegylated interferon alfa-2a (peg-IFN alfa-2a), pegIFN alfa-2b, albinterferon alfa-2b, telaprevir, and boceprevir. The majority of the 13,599 participants were genotype 1 (N = 11,730), while genotype 2 (N = 783) and genotype 3 (N = 995) made up most of the remainder. In addition to assessing SVR12, the authors also reviewed the predictive value of SVR4 with respect to SVR24.

SVR12 was achieved by 51.8% (7,051 of 13,599 patients) and SVR24 by 50.6% (6,881 of 13,599 patients) of adults in the database.[36] 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.[36] 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 IFN plus ribavirin.[36] Further monitoring of IFN-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.[38] This study included 781 patients with CHC; all had received pegylated interferon plus ribavirin (PR). 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.[38] 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.[39] The authors pooled single-arm data for pegIFN 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 pegIFN 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 pegIFN. The authors concluded that SVR12 was 5% to 6% higher than SVR24, although the credible intervals overlapped in the conventional meta-analysis, and in the Bayesian meta-regression the credible intervals included the null value (SVR12 versus SVR24, relative risk 1.13; 95% credible interval, 0.99 to 1.26).[39] 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 to determine comparative efficacy, as it ignores the benefits of randomization and may therefore be subject to the same biases as a comparison of independent cohort studies. In addition, the analysis was limited to data from patients who received PR, and did not examine the concordance of SVR12 and SVR24 among those who received a DAA regimen.

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).[40] 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) 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, pain, vitality, social functioning, psychological functioning, general health perceptions (GH), and role limitations due to physical and emotional problems. SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS). The PCS, 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.[37]

A systematic review was conducted to identify and provide information on HRQoL instruments for HCV infection.[41] The authors identified 32 studies and presented the results by types of clinical anchors (for example, HCV 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 HCV status (the clinical anchor). Patients with HCV infection scored lower on the various domains than healthy patients. The largest impact of the disease was on role physical, role emotional, and general health (Table 19).[41]
- A panel of experts was convened to indirectly estimate the minimal clinically important difference (MCID) in hepatitis C based upon existing HRQoL data.[41] 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).[41] MCIDs for other dimensions or for the two component scores were not estimated. Of note, this study did not use the preferred methods to generate the MCID, and it is unclear whether the estimates represent values patients would identify as clinically important.

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

TABLE 19: SF-36: HEPATITIS C PATIENT VERSUS HEALTHY CONTROL WEIGHTED MEAN AND MEDIAN CROSS-SECTIONAL DIFFERENCE (15 STUDIES)

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

SF-36 = Short-Form (36) Health Survey

Summary

- A review using individual patient data from 15 phase 2 and 3 studies (N = 13,599 participants), in which the majority were patients with 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 patients with hepatitis C. 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.

APPENDIX 6: ADDITIONAL EVIDENCE FROM CLINICAL TRIALS NOT INCLUDED IN THE SYSTEMATIC REVIEW – STUDY 031

Aim

To summarize the non-randomized, open-label (OL), single-group, relapser cohort arm in Study AI447-031 (Study 031).[13] This cohort was excluded from the systematic review because it was a non-randomized cohort.

Summary of Study 031

Study 031[13] was a phase 3, comparative study of daclatasvir (DCV) plus asunaprevir (ASV) combination therapy versus telaprevir (TEL) therapy in Japanese patients with genotype 1b chronic hepatitis C (CHC) who were interferon (IFN) eligible-naive, and a single-arm assessment of DUAL Therapy DCV + ASV in IFN-therapy relapsers.[13]

Study Characteristics

Study 031 was an OL study for patients with genotype 1b hepatitis C virus (HCV) and was divided into two cohorts: the IFN-eligible naive cohort and the relapser cohort. The inclusion criteria in the relapser cohort in Study 031 were patients aged 20 to 75 years with genotype 1b CHC, who relapsed following IFN-containing therapy (except TEL and pegylated interferon plus ribavirin [PR]). Characteristics of Study 031 are summarized in Table 7.

Study Patients

Among patients included in the relapser cohort, 21 out of 22 patients completed treatment; one patient did not complete the treatment period due to adverse events. The demographic characteristics of the patients included in the relapser cohort are presented in Table 20. The median age was 64.5 years; 68.2% of the patients were female; and all patients had a viral load ≥ 800,000 IU/mL at baseline.

TABLE 20: BASELINE CHARACTERISTICS IN RELAPSER ARM IN STUDY 031

	Study 031
	DCV + ASV 24 weeks
	Relapsed patients after IFN-based therapy
N	22
Age — years, median (range)	64.5 (45 to 75)
Male, n (%)	7 (32)
HCV genotype, n (%)	
Genotype 1b	22 (100)
Cirrhosis or METAVIR F4, n (%)	1 (4.5)
Baseline HCV RNA, log10 IU/mL, mean (SD)	7.0 (0.5)
Baseline HCV RNA, n (%)	
< 800,000 IU/mL	0
≥ 800,000 IU/mL	22 (100)
Previous response to HCV treatment	
Relapse	22 (100)

	Study 031
	DCV + ASV 24 weeks
	Relapsed patients after IFN-based therapy
Prior HCV treatment	
IFN regimen	22 (100)
DAA regimen	NR

ASV = asunaprevir; DAA = direct-acting antiviral; DCV = daclatasvir; HCV = hepatitis C virus; IFN = interferon; METAVIR = Meta-analysis of Histological Data in Viral Hepatitis; NR = not reported; RNA = ribonucleic acid; SD = standard deviation.
Source: Clinical Study Report.[13]

Efficacy Results

For patients receiving DCV + ASV for 24 weeks, sustained virologic response 12 weeks after the end of treatment (SVR12) was achieved by 21/22 (95.5%) patients. One of the 22 patients (4.5%) relapsed during the follow-up period.

The mean baseline score on the Short-Form (36) Health Survey (SF-36) physical component summary (PCS) — in which higher scores indicate better quality of life in areas of physical functioning — was 53.19 in the relapser cohort. After 12 weeks of treatment, the mean score of PCS decreased by –1.65 from baseline. At 12 weeks post-treatment, the PCS score was comparable with baseline levels (53.04 in the relapser cohort). A similar pattern was observed for the mental component summary (MCS), in which higher scores indicated better quality of life in areas of mental functioning. The mean baseline score of MCS was 49.76. The mean score of MCS increased by 3.57 from baseline to week 12. At 12 weeks post-treatment, the PCS score was comparable with baseline levels (51.01 in the relapser cohort).

Safety Results

Adverse events were reported in 81.8% of patients; one adverse event was classified as serious (Table 21). One adverse event led to drug discontinuation. There were no deaths. Key safety results in the relapser cohort were generally consistent with those in the IFN-eligible naive cohort DCV + ASV arm. The most common (> 10%) events reported in the relapser cohort were nasopharyngitis (27.3%), malaise (27.3%), diarrhea (13.6%), increased alanine aminotransferase (ALT) (18.2%), increased aspartate aminotransferase (AST) (18.2%), pyrexia (13.6%), and contusion (13.6%). Rash composite events were reported for 2 (9.1%) patients.

TABLE 21: SUMMARY OF OUTCOMES IN RELAPSER ARM IN STUDY 031

Outcome/Subgroup	Study 031 Genotype 1b Treatment-Naive	
	DCV + ASV 24 weeks	
	n/N	**% (95% CI)**
SVR12 (mITT)	21/22	95.5% (77 to 100)
On-treatment failure[b]	0/22	0
Relapse	1/22	4.5%
Adverse events		
Any adverse events	18	81.8%
Any serious adverse events	1	4.5%

Outcome/Subgroup	Study 031 Genotype 1b Treatment-Naive	
	DCV + ASV 24 weeks	
	n/N	% (95% CI)
Adverse events leading to drug discontinuation	1	4.5%
Death	0	0

ASV = asunaprevir; DCV = daclatasvir; CI = confidence interval; mITT = modified intention-to-treat; N = number of patients; SVR12 = sustained virologic response 12 weeks after the end of treatment.
Source: Clinical Study Report.[13]

APPENDIX 7: ADDITIONAL EVIDENCE FROM CLINICAL TRIALS NOT INCLUDED IN THE SYSTEMATIC REVIEW — QUADRIH STUDY

Aim

To summarize the non-randomized, open-label (OL), single-group ANRS HC30 QUADRIH study (QUADRIH) in patients with HIV and hepatitis C virus (HCV) coinfection.[42] This study was excluded from the systematic review because it was a non-randomized trial.

Study Characteristics

Patients aged 18 years or older, with chronic hepatitis C (CHC) genotype 1 or 4 infection (with or without cirrhosis) and HIV were enrolled in this OL, non-randomized study. All patients had a prior null response to pegylated interferon plus ribavirin (PR) therapy and were on stable antiretroviral therapy (ART) that included raltegravir backbone combined with two nucleoside analogues among tenofovir, emtricitabine, abacavir, and lamivudine. Enfuvirtide could be added if needed.

Patients were excluded if they had Child B or C cirrhosis, or a history of decompensated cirrhosis, prior HCV therapy with nonstructural protein 3 (NS3) protease inhibitors, hepatitis B coinfection, prior transplant, ongoing malignant disease, or an addiction that might interfere with study participation.

All patients received four weeks of PR therapy (pegylated interferon alfa-2a 180 mcg/week plus weight-based ribavirin 1,000 mg to 1,200 mg per day), then PR plus daclatasvir (DCV) 60 mg daily and asunaprevir (ASV) 100 mg twice daily, for an additional 24 weeks. The primary outcome was sustained virologic response 12 weeks after the end of treatment (SVR12), and secondary outcomes included virologic response and harms. The study was powered to detect a 20% difference in SVR12 rates, compared with a historical 40% response rate (based on previous studies of boceprevir or telaprevir plus PR) in patients with prior null response to PR.

The study was conducted in multiple sites in France. Bristol-Myers Squibb provided some funding and technical support to the study.

Study Patients

A total of 75 patients were enrolled and treated, and of these, 36% had cirrhosis at baseline. The median age was 50 years and the majority of participants were male (Table 22).

TABLE 22: BASELINE CHARACTERISTICS FOR QUADRIH STUDY

	DCV/ASV + PR[a] 24 weeks
N	75
Age — years, median (IQR)	50 (48 to 53)
Male, n (%)	59 (79)
HCV genotype, n (%)	
Genotype 1	37 (49)
Genotype 4	38 (51)
Cirrhosis or METAVIR F4, n (%)	27 (36)

	DCV/ASV + PR[a] 24 weeks
Baseline HCV RNA, log10 IU/mL, median (IQR)	6.06 (5.75 to 6.58)
HIV viral load < 50 cp/mL, n (%)	69 (92)
CD4/mm³, median (IQR)	748 (481 to 930)

ASV = asunaprevir; cp = copies; DCV = daclatasvir; HCV = hepatitis C virus; IQR = interquartile range; METAVIR = Meta-analysis of Histological Data in Viral Hepatitis; PR = pegylated interferon plus ribavirin; RNA = ribonucleic acid.
[a] Four weeks of PR therapy prior to DCV/ASV + PR treatment.
Source: Piroth.[42]

Efficacy Results

Overall, 73 (96%) of patients achieved SVR12, and the response rate was similar for patients with genotype 1 or 4, and for those with or without cirrhosis (Table 23). Two patients (3%) experienced a virologic breakthrough during treatment, and no patients relapsed.

The SVR12 rates observed in this trial were similar to those reported for the QUAD study, which enrolled treatment-experienced genotype 1 and 4 CHC patients without HIV coinfection.

TABLE 23: SUMMARY OF OUTCOMES FOR QUADRIH STUDY

Outcome/Subgroup	DCV/ASV + PR 24 weeks[a]	
	n/N	**% (95% CI)**
SVR12 (ITT)	72/75	96% (89 to 99%)
Subgroup by fibrosis severity		
Cirrhosis	25/27	93% (76 to 99%)
No Cirrhosis	47/48	98% (89 to 100%)
Subgroup by genotype		
Genotype 1	35/37	95% (82 to 99%)
Genotype 4	37/38	97% (86 to 100%)
On-treatment failure	2/75	3%
Relapse	0	0%
Adverse events		
Any adverse events	73/75	97%
Any serious adverse events	21/75	28%
Adverse events leading to drug discontinuation	3/75	4%
Death	1/75	1%

ASV = asunaprevir; CI = confidence interval; DCV = daclatasvir; ITT = intention-to-treat; N = number of patients; PR = pegylated interferon plus ribavirin; SVR12 = sustained virologic response 12 weeks after the end of treatment.
[a] Four weeks of PR therapy prior to DCV/ASV + PR treatment.
Source: Piroth.[42]

Safety Results

As summarized in Table 23, most patients (97%) experienced an adverse event, the most common of which were fatigue or asthenia (73%), anemia (35%), neutropenia (32%), dry skin (24%), decreased appetite (23%), flu-like symptoms (23%), and diarrhea (21%). The incidence of serious adverse events was higher in the QUADRIH study (28%) than in QUAD (6%). During QUADRIH, a total of 36 serious adverse events occurred in 21 patients (28%). These included serious hematological (15%), infectious (5%), gastrointestinal (3%), and hepatobiliary (3%) events. Four per cent of patients stopped therapy due to adverse events.

Summary

In the QUADRIH study, 75 patients with HIV and genotype 1 or 4 CHC (prior null response to PR) were treated with open-label DCV/ASV + PR for 24 weeks. In this non-randomized study, patients with and without cirrhosis achieved SVR12 response rates that exceeded 90%; however, the incidence of serious adverse events was also high (28%) compared with the other DCV/ASV + PR trial.

The trial was limited by the lack of randomization and comparator groups, small sample size (N = 75), and potential bias in the reporting of adverse events due to the lack of blinding. The study restricted enrolment to patients on specific antiretroviral treatment regimens, which may limit generalizability.

APPENDIX 8: SUMMARY AND CRITICAL APPRAISAL OF MANUFACTURER-PROVIDED INDIRECT TREATMENT COMPARISON

Aim

This brief provides a summary and critical appraisal of the methods and main findings of the network meta-analysis (NMA) for treatment-naive patients with hepatitis C virus (HCV) genotype 1b, and the matching-adjusted indirect comparisons (MAIC) for treatment-naive and treatment-experienced patients with HCV genotype 1b, which was submitted by the manufacturer.[31]

Summary of the Indirect Treatment Comparisons

Due to the lack of randomized controlled trials (RCTs) directly comparing the daclatasvir (DCV) and asunaprevir (ASV) regimen versus other regimens of interest in patients chronically infected with HCV, indirect comparison and NMA was performed in patients with genotype 1b chronic hepatitis C (CHC). The outcomes assessed were sustained virologic response (SVR), discontinuation due to adverse events, and events of special interest, such as anemia, and rash.

Three indirect treatment comparisons (ITCs) (one Bayesian NMA and two MAIC) were performed to estimate the comparative efficacy and safety of DCV + ASV with boceprevir (BOC), telaprevir (TEL), simeprevir (SIM), or sofosbuvir (SOF) in combination with pegylated interferon plus ribavirin (PR), or PR alone. NMAs can be conducted when trials of different treatments can be linked together via randomized comparisons to the same reference treatment. Then NMA synthesizes the direct and indirect evidence for each possible pairwise treatment comparison across included trials. In the case of hepatitis C trials for newer interferon-free treatments, comparative trials with common reference arms are limited. When common reference arms are not available, anchor-based indirect comparisons, including network meta-analyses, cannot be conducted. In these situations, the manufacturer used MAIC to compare outcomes between trials while adjusting for baseline differences in trial populations. The MAIC method was used in order to adjust for cross-trial differences in baseline characteristics.

Methods

Eligibility Criteria

Inclusion criteria for the review consisted of the following: phase 3 clinical trials in adult treatment-naive and treatment-experienced genotype 1 CHC patients, treated with either SIM, SOF, BOC, or TEL plus PR. Included trials were required to report rates of SVR for subgroups of patients infected with HCV genotype 1b. The outcomes of interest were SVR and adverse events.

Indirect Treatment Comparisons

The authors analyzed data using two approaches: one approach was the conventional NMA, which was applied to treatment-naive patients to compare DCV + ASV versus BOC, TEL, SIM, or SOF in combination with PR, or PR alone for SVR12 or SVR24, and safety outcomes of discontinuation due to adverse event and rates of anemia and rash. Pairwise comparative estimates between treatments were reported as odds ratios (ORs) and rate differences. The NMA was fitted using a fixed-effects model; vague priors were to ensure that treatment comparisons were driven by the observed data. Only treatment-naive TEL + PR, BOC + PR, SIM + PR, and SOF + PR trials with a PR treatment arm were included in the NMA.

The second approach used the MAIC method to incorporate data from single-arm studies into the ITC. Individual patient-level data were used in trials of DCV + ASV from trial arms of treatment-naive and treatment-experienced genotype 1b patients. A propensity model was estimated to describe each patient's odds of enrolment in the trial with individual patient data (IPD) as opposed to the comparator trial(s) without IPD. Thus, patient types under-represented in the IPD versus the comparator trials were up-weighted to compensate, and vice versa. After weighting, the average (or median) values of baseline characteristics were balanced between the trial populations, which included age, body mass index (BMI), gender, race, genotype subtype, IL28B, plasma HCV ribonucleic acid (RNA) level, alanine aminotransferase (ALT) level, and presence or absence of cirrhosis. In the event that there were differences in the inclusion and exclusion criteria between a trial and the comparator trial(s) identified in the systematic literature review, patients enrolled in the analyzed trial were subject to the inclusion and exclusion criteria reported in the comparator trial(s) wherever possible. Specifically, patients enrolled in the analyzed trial were excluded from the analysis if any of the inclusion criteria were broader or the exclusion criteria were narrower than those of the comparator trial(s).

Multiple imputations were used to address the missing subgroup genotype 1b baseline data from the comparator trials. Three sources of information were used to construct an informative, empirically based prior distribution for the missing baseline data in the genotype 1b subgroup: 1) the numbers and proportions of patients with genotypes 1a and 1b; 2) the pooled mean vector of baseline characteristics; and 3) the IPD from trials that included both genotype 1a and 1b, which were used to indicate the associations between genotype and other baseline characteristics. Studies with dosing not consistent with the Food and Drug Administration (FDA) label were excluded from the MAIC analysis. Treatment arms with the same regimens from different trials were pooled together.

Included Studies

Individual patient-level data were drawn from the manufacturer-sponsored trials of DCV + ASV, while systematic literature reviews were conducted to identify phase 3 clinical trials of the TEL + PR, BOC + PR, SIM + PR, or SOF + PR regimens in treatment-naive and treatment-experienced genotype 1 patients.

A total of seven trials were included in the core NMA for treatment-naive patients: DCV + ASV versus TEL + PR (one randomized controlled trial [RCT]); TEL + PR versus PR (one RCT); SIM + PR versus PR (one RCT); and BOC + PR versus PR (one RCT). A sensitivity analysis was undertaken in which one phase two study comparing SOF + PR with PR was included in the NMA.

A total of nine trials were included in the MAIC analyses for treatment-naive patients: DCV + ASV (two trials); TEL + PR (three trials); SIM + PR (two trials); BOC + PR (one trial); and SOF + PR (one trial).

A total of six trials were included in the MAIC analyses for treatment-experienced patients: DCV + ASV (three trials); TEL + PR (one trial); SIM + PR (one trial); and BOC + PR (one trial).

Enrolment criteria were similar between all trials with the exception that the DCV + ASV trial AI447-028 (DUAL) enrolled patients with HCV RNA ≥ 10,000 IU/mL or higher at baseline and trials AI447-031 and AI447-026 (NIPPON) enrolled patients with HCV RNA level ≥ 100,000 IU/mL at baseline, whereas the TEL trials enrolled patients with HCV RNA > limit of detection or > 1,000 IU/mL and the BOC, SIM, and SOF trials enrolled patients with HCV RNA ≥ 10,000 IU/mL. In addition, trial AI447-031 of DCV + ASV excluded patients with evidence of cirrhosis by liver biopsy or non-invasive assessment of fibrosis serum markers within 36 months before screening, whereas other comparator trials did not. However, approximately

5% of patients treated with DCV + ASV in AI447-031 had advanced fibrosis, based on FibroTest scores at baseline.

Results

The results of the NMA in treatment-naive patients with genotype 1b CHC are presented in Table 24. Estimates were interpreted as statistically significantly different if the 95% credible intervals (CrIs) of the OR did not include the null value of 1, or the 95% CrI of the rate difference did not include the null value of 0.

The SVR rates achieved with DCV + ASV in treatment-naive patients with genotype 1b were statistically significantly higher than PR, TEL + PR, BOC + PR, and SIM + PR. In the sensitivity analysis that included the phase 2 trial of SOF + PR, SVR rates achieved with DCV + ASV were still statistically significantly higher than PR, TEL + PR, BOC + PR, and SIM + PR; however, there was no statistically significant difference in SVR rates between DCV + ASV and SOF + PR.

DCV + ASV treatment was associated with statistically significantly lower rates of anemia, rash, and discontinuation due to adverse events compared with PR and TEL + PR, and significantly lower rates of anemia and rash compared with BOC + PR and SIM + PR.

TABLE 24: NETWORK META-ANALYSIS RESULTS FOR DACLATASVIR + ASUNAPREVIR IN TREATMENT-NAIVE PATIENTS WITH GENOTYPE 1B CHRONIC HEPATITIS C

Outcome/Treatment	% Patients With Outcome[a]			Odds Ratio DCV + ASV Versus Comparator		Rate Difference (%) DCV + ASV Versus Comparator	
	Posterior median		95% CrI	Posterior median	95% CrI	Posterior median	95% CrI
SVR —core analysis[b]							
DCV + ASV	94.53		(88.64 to 97.56)	--	--	--	--
PR	48.86		(45.41 to 52.33)	18.1	(8.3 to 41.3)	45.48	(39.46 to 49.95)
TEL + PR	77.32		(69.20 to 83.90)	5.1	(2.6 to 10.5)	16.90	(11.03 to 23.85)
BOC + PR	73.63		(62.41 to 82.64)	6.2	(2.4 to 16.2)	20.61	(10.39 to 32.26)
SIM + PR	83.30		(76.49 to 88.52)	3.5	(1.4 to 8.7)	11.04	(3.70 to 18.49)
SVR — sensitivity analysis (including SOF + PR phase 2 trial)							
DCV + ASV	94.6		(88.9 to 97.6)	--	--	--	--
PR	49.3		(45.8 to 52.8)	18.10	(8.30 to 41.50)	NR	NR
TEL + PR	77.6		(70.0 to 84.1)	5.07	(2.59 to 10.51)	NR	NR
BOC + PR	74.0		(62.8 to 82.8)	6.19	(2.44 to 16.26)	NR	NR
SIM + PR	83.5		(76.8 to 88.7)	3.47	(1.43 to 8.73)	NR	NR
SOF + PR	89.2		(70.0 to 97.2)	2.14	(0.42 to 9.57)	NR	NR
AEs							
Discontinuation due to AE	DCV + ASV	2.1	NR	--	--	--	--
	PR	9.6	NR	NR	NR	–7.42	(–9.36 to –3.61)
	TEL + PR	9.5	NR	NR	NR	–7.17	(–12.57 to –3.62)
	BOC + PR	7.1	NR	NR	NR	–4.77	(–11.41 to 0.16)
	SIM + PR	7.8	NR	NR	NR	–5.54	(–18.33 to 0.49)
Anemia	DCV + ASV	0	NR	--	--	--	--
	PR	33.8	NR	NR	NR	–33.80	(–36.98 to –30.78)
	TEL + PR	59.1	NR	NR	NR	–59.08	(–69.89 to –47.59)

Outcome/Treatment	% Patients With Outcome[a]			Odds Ratio DCV + ASV Versus Comparator		Rate Difference (%) DCV + ASV Versus Comparator	
	Posterior median		95% CrI	Posterior median	95% CrI	Posterior median	95% CrI
	BOC + PR	54.6	NR	NR	NR	–54.52	(–67.22 to –41.42)
	SIM + PR	29.5	NR	NR	NR	–29.51	(–38.82 to –21.64)
Rash	DCV + ASV	1.7	NR	--	--	--	--
	PR	28.9	NR	NR	NR	–27.07	(–30.16 to –23.88)
	TEL + PR	41.0	NR	NR	NR	–39.10	(–48.90 to –30.02)
	BOC + PR	31.7	NR	NR	NR	–29.78	(–43.74 to –18.49)
	SIM + PR	27.2	NR	NR	NR	–25.32	(–34.02 to –18.05)

AE = adverse event; ASV = asunaprevir; BOC = boceprevir; DCV = daclatasvir; CrI = credible interval; NMA = network meta-analysis; NR = not reported; PR = pegylated interferon plus ribavirin; SIM = simeprevir; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; TEL = telaprevir.

[a] Percentage stands for the percentage of patients achieving SVR, or percentage of patients who discontinued due to AE, or with anemia or rash.

[b] Either SVR12 or SVR24.

Source: CADTH Common Drug Review submission.[31]

The results of the MAIC procedure for treatment-naive patients are presented in Table 25; these analyses are pairwise comparison of two treatments at a time. Estimates were interpreted as statistically significantly different if the 95% confidence interval (CI) of the adjusted mean difference in proportion of patients with the outcome did not include the null value of 0.

After adjustment with multiple imputation and matching, treatment-naive patients with genotype 1b who were treated with DCV + ASV achieved statistically significantly higher SVR rates than patients treated with PR, TEL + PR, and BOC + PR. No statistically significant differences in SVR rates were observed among patients treated with DCV + ASV when compared with those treated with SOF + PR or SIM + PR. After adjustment with multiple imputation and matching, patients treated with DCV + ASV had statistically significantly lower rates of discontinuation due to AEs, anemia, and rash than PR alone or in combination with TEL or BOC. When compared with patients treated with SIM + PR, those treated with DCV + ASV had statistically significantly lower adjusted rates of anemia and rash. Discontinuation due to adverse events did not significantly differ between the two groups. DCV + ASV also had lower rates of anemia than SOF + PR. Discontinuation due to adverse events and rash were not significantly different between these two groups.

TABLE 25: MAIC RESULTS FOR DACLATASVIR + ASUNAPREVIR IN TREATMENT-NAIVE PATIENTS WITH GENOTYPE 1B CHRONIC HEPATITIS C

Outcome/Comparator	% Patients With Outcome[a]		Difference (%) DCV + ASV Versus Comparator	
	Comparator	Adjusted DCV + ASV	Adjusted mean difference	95% CI
SVR				
PR[b]	47.0	86.6	39.6	(30.3 to 48.9)
TEL + PR[c]	77.9	86.6	8.7	(0.2 to 17.3)
BOC + PR[c]	66.4	82.9	16.5	(2.5 to 30.5)
SIM + PR[b]	85.4	85.8	0.4	(–8.9 to 9.7)
SOF + PR[b]	81.8	84.8	3.0	(–21.2 to 27.1)

Outcome/Comparator		% Patients With Outcome[a]		Difference (%) DCV + ASV Versus Comparator	
		Comparator	Adjusted DCV + ASV	Adjusted mean difference	95% CI
AEs					
Discontinuation due to AE	PR	8.7	1.7	–7.0	(–10.2 to –3.7)
	TEL + PR	15.6	1.5	–14.2	(–17.6 to –10.8)
	BOC + PR	12.2	4.2	–8.1	(–15.1 to –1.0)
	SIM + PR	1.7	1.5	–0.2	(–2.5 to 2.1)
	SOF + PR	1.5	0.9	–0.6	(–4.4 to 3.1)
Anemia	PR	24.4	0	–24.4	(–28.4 to –20.4)
	TEL + PR	39.9	0	–39.9	(–43.7 to –36.0)
	BOC + PR	49.5	0	–49.5	(–57.3 to –41.7)
	SIM + PR	20.3	0	–20.3	(–25.2 to -15.5)
	SOF + PR	20.8	0	–20.8	(–30.0 to –11.5)
Rash	PR	24.3	1.4	–22.9	(–27.3 to –18.6)
	TEL + PR	36.3	2.0	–34.3	(–38.6 to –29.9)
	BOC + PR	25.3	2.5	–22.8	(–30.5 to –15.0)
	SIM + PR	30.3	1.4	–28.9	(–34.7 to –23.2)
	SOF + PR	18.0	12.7	–5.3	(–27.8 to 17.2)

AE = adverse event; ASV = asunaprevir; BOC = boceprevir; CI = confidence interval; DCV = daclatasvir; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; NR = not reported; PR = pegylated interferon plus ribavirin; SIM = simeprevir; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; TEL = telaprevir.

[a] Percentage stands for the percentage of patients achieving SVR, or percentage of patients who discontinued due to AE, or with anemia or rash.

[b] SVR12.

[c] SVR24

Source: CADTH Common Drug Review submission.[31]

The results of the MAIC procedure for treatment-experienced patients are presented in Table 26; these analyses are disjointed analyses of two treatments at a time. Estimates were interpreted as statistically significantly different if the 95% CI of the RD did not include the null value of 0.

After adjustment with multiple imputations and across baseline characteristics, treatment with DCV + ASV provided statistically significantly higher SVR rates among previous non-responders than PR alone or in combination with BOC, TEL, or SIM. DCV + ASV was also associated with higher SVR rates in all prior response categories than PR alone or in combination with TEL or BOC. After adjustment with multiple imputation and matching, rates of anemia and rash were statistically significantly lower in patients treated with DCV + ASV than in patients treated with TEL + PR, BOC + PR, SIM + PR, and PR alone. Discontinuation due to adverse events did not statistically significantly differ between DCV + ASV and comparator regimens.

TABLE 26: MAIC RESULTS FOR DACLATASVIR + ASUNAPREVIR IN TREATMENT-EXPERIENCED PATIENTS WITH GENOTYPE 1B CHRONIC HEPATITIS C

Outcome/Comparator		% Patients With Outcome[a]		Difference (%) DCV + ASV Versus Comparator	
		Comparator	Adjusted DCV + ASV	Adjusted mean difference	95% CI
SVR					
PR trial baseline population[b]		36.2	93.8	57.7	(44.0 to 71.4)
PR estimated subpopulation: partial responders[b]		9.1	81.0	71.9	NR
PR estimated subpopulation: relapsers[b]		41.3	96.3	55.0	NR
TEL trial baseline population[b]		73.3	90.3	17.0	(5.3 to 28.7)
TEL estimated subpopulation: null responders[b]		38.4	83.4	44.9	NR
TEL estimated subpopulation: partial responders[b]		68.7	83.0	14.3	NR
TEL estimated subpopulation: relapsers[b]		88.4	95.7	7.2	NR
BOC trial baseline population[c]		65.3	88.1	22.8	(6.9 to 38.7)
BOC estimated subpopulation: partial responders[c]		48.8	76.6	27.8	NR
BOC estimated subpopulation: relapsers[c]		75.4	95.2	19.8	NR
SIM (relapsers)[b]		85.9	96.2	10.3	(1.1 to 19.5)
AEs					
Discontinuation due to AE	PR	0.9	1.0	0.1	(–2.8 to 2.9)
	TEL + PR	6.4	14.8	8.4	(–3.4 to 20.1)
	BOC + PR	8.0	14.1	–3.9	(–13.2 to 5.3)
	SIM + PR	0.4	7.2	6.8	(–5.1 to 18.7)
Anemia	PR	20.2	0	–20.2	(–27.4 to –12.9)
	TEL + PR	30.0	0.1	–29.9	(–38.3 to –21.5)
	BOC + PR	43.2	0.0	–43.2	(–53.9 to –32.5)
	SIM + PR	16.9	0	–16.9	(–29.2 to –15.1)
Rash	PR	16.0	1.0	–15.0	(–22.0 to –8.0)
	TEL + PR	37.0	19.0	–18.0	(–33.5 to –2.5)
	BOC + PR	16.7	4.2	–12.5	(–23.2 to –1.7)
	SIM + PR	23.1	0.9	–22.2	(–29.2 to –15.1)

AE = adverse event; ASV = asunaprevir; BOC = boceprevir; CI = confidence interval; DCV = daclatasvir; NMA = network meta-analysis; NR = not reported; PR = pegylated interferon plus ribavirin; SIM = simeprevir; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; TEL = telaprevir.

[a] Percentage stands for the percentage of patients achieving SVR, or percentage of patients who discontinued due to AE, or with anemia or rash.

[b] SVR12.

[c] SVR24.

Source: CADTH Common Drug Review submission.[31]

Critical Appraisal

Critical Appraisal of the Network Meta-Analysis

The NMA was appraised using the National Institute for Health and Care Excellence (NICE) Decision Support Unit Reviewer's Checklist.[43] The NMA did not satisfactorily meet the checklist's criteria on several items (Table 27).

The scope of the NMA was limited to evaluating efficacy in treatment-naive CHC patients with genotype 1b. The authors did not assess efficacy and safety in patients previously treated with PR or another DAA regimen.

Several limitations of the NMAs were noted, with key considerations as follows:

- The methods used to screen and extract data from studies were not reported (i.e., there was no mention of independent screening by two reviewers).
- It appears there was no assessment of the risk of bias of the included studies or an assessment of publication bias.
- The manufacturer-submitted NMA excluded two interferon-free regimens — ledipasvir (LDV)/SOF and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin — which were recently approved by Health Canada and indicated for treatment-naive and treatment-experienced patients with HCV genotype 1. However, at the time when the literature search was conducted for this ITC, these regimens had not been approved by Health Canada.
- Different treatment durations were pooled together and analyzed in the NMA as one node; hence, we are not able to estimate the effect of solely the Health Canada–approved treatment duration.
- Doses not approved by Health Canada were included in the NMA.
- It was unclear which data were included in the analyses, as no SVR or adverse event data from individual trials were reported.
- No information was reported related to model fit, assessment of model convergence, or inconsistency.
- It appears that there was no assessment of heterogeneity across trials. Japanese studies using lower doses than that recommended in Canada were included in the analyses; thus, the trials included in the analyses were not similar, especially from a dosage perspective, for some regimens.

Critical Appraisal of the MAIC

A major strength of the MAIC method is that it makes use of the individual patient-level data by applying a weighting method, and as a result, it ensures that potential confounding variables were matched between the treatment arms of manufacturer-sponsored trials with that of the comparison arm from selected published trials.

The MAIC methods were also well reported, in that structured tables to show data available from the IPD/aggregate trials were provided, demographics between groups were compared, the report was transparent when limited data were available, and the further steps taken for MAIC to adjust for missing data were explained.

There are several weaknesses to this method. In the literature, the MAIC technique has been used by only one person (i.e., the author who “invented” it and also led this submission) and so the technique has not been the subject of any empirical or methods research. In addition, there is currently uncertainty as to the performance of MAIC techniques for ITCs. This approach has not been empirically assessed in the peer-reviewed literature, and thus its strengths and weaknesses still require investigation by the research community. In general, it seems that most aspects one could consider critically appraising have been discussed satisfactorily, except for the few limitations highlighted.

The validity of the estimates is also uncertain, due to several limitations in the methodology. Only two treatments can be compared at a time, which makes it difficult to assess the comparative effectiveness of a class of drugs. After adjusting for baseline characteristics, a naive indirect comparison of single-arm data was undertaken using disjoint analyses of two treatments at a time. Therefore, randomization has not been preserved and could result in biased estimates of treatment effect.

In the analysis of patients with genotype 1b, multiple imputation methods were used to address the missing genotype 1b baseline data from the comparator trials and to account for the additional uncertainty in the comparative analyses due to these missing data. After these adjustments, the MAIC technique was applied. This procedure would include many adjustments, and response rates might not be accurate as a result. Furthermore, treatment arms with the same regimens from different trials were pooled together, with no adjustment for baseline characteristics. Pooling these patients together may not be appropriate, as differences in baseline characteristics may contribute to differences in response rates.

The MAIC method reduces sample size, which further compromises the already constrained precision of estimates on comparative efficacy and, rare, safety events.

No comparison was made for DCV/ASV + PR versus other regimens for patients with genotype 1 and genotype 4; hence, the efficacy of DCV/ASV + PR in comparison with other regimens is not known in these genotypes.

Finally, the manufacturer-submitted ITC excluded two interferon-free regimens — LDV/SOF and ombitasvir/paritaprevir/ritonavir + dasabuvir with or without ribavirin — both of which were recently approved by Health Canada and indicated for treatment-naive and treatment-experienced patients with HCV genotype 1. Thus, it is not possible to know the efficacy of DCV + SOF, DCV + ASV, or DCV/ASV + PR versus these interferon-free regimens.

Summary

The manufacturer submitted a Bayesian NMA that estimated the comparative efficacy of DCV + ASV with BOC, TEL, SIM, or SOF in combination with PR, or PR alone, in treatment-naive patients with genotype 1b CHC infection. Data from seven trials were incorporated into the model. The odds of achieving SVR were higher for DCV + ASV than for PR and for the other DAA + PR regimens. DCV + ASV treatment was associated with statistically significantly lower rates of anemia, rash, and discontinuation due to adverse events compared with PR and TEL + PR, and significantly lower rates of anemia and rash compared with BOC + PR and SIM + PR.

The manufacturer submitted two ITCs using the MAIC technique. This method was used to incorporate individual patient-level data from single-arm studies in order to adjust for differences in baseline patient characteristics across separate study populations. With this method, in treatment-naive with genotype 1b patients, DCV + ASV was associated with statistically significantly higher SVR rates than patients treated with PR, TEL + PR, and BOC + PR, but not statistically significant better than SOF + PR and SIM + PR. DCV + ASV had also statistically significantly lower rates of discontinuation due to adverse events, anemia, and rash than PR alone or in combination with TEL or BOC. For treatment-experienced patients with genotype 1b, DCV + ASV provided statistically significantly higher SVR rates among previous non-responders than PR alone or PR in combination with BOC, TEL, or SIM. In addition, rates of anemia and rash were statistically significantly lower in patients treated with DCV + ASV than in patients treated with TEL + PR, BOC + PR, SIM + PR, and PR alone.

An important limitation of these ITCs is the absence of comparisons against two recently approved interferon-free regimens: LDV/SOF and ombitasvir/paritaprevir/ritonavir + dasabuvir with or without ribavirin. As with any indirect comparison, cross-trial differences in confounding factors could affect outcomes and lead to bias. In addition (as noted above), there remains uncertainty as to the validity of incorporating single-arm data in Bayesian NMAs, as well as regarding the optimal methodological

approach. Finally, it is also worth noting that there is currently uncertainty as to the performance of MAIC techniques for ITCs. This approach has not been empirically assessed in the peer-reviewed literature, and thus its strengths and weaknesses still require investigation by the research community.

TABLE 27: CRITICAL APPRAISAL OF THE NETWORK META-ANALYSIS CHECKLIST

Table		Item Satisfactory?	Comments
A. DEFINITION OF THE DECISION PROBLEM ***A1. Target population for decision***			
A1.1	*Has the target patient population for decision been clearly defined?*	Partial	The population is clearly defined (treatment-naive genotype 1b CHC) but is incomplete. DCV + ASV is also indicated for those who failed prior treatment with PRs.
A2. Comparators			
A2.1	*Decision Comparator Set: Have all the appropriate treatments in the decision been identified?*	No	Two interferon-free regimens, ledipasvir + sofosbuvir and ombitasvir/paritaprevir/ritonavir, are approved by Health Canada and indicated for treatment-naive and treatment-experienced patients with HCV genotype 1.
A2.2	*Synthesis Comparator Set: Are there additional treatments in the Synthesis Comparator Set that are not in the Decision Comparator Set? If so, is this adequately justified?*	Yes	No additional treatments were included in the synthesis set.
A3 Trial inclusion / exclusion			
A3.1	*Is the search strategy technically adequate and appropriately reported?*	Partial	Unclear whether study screening was done independently by 2 reviewers. The search included multiple databases. Unclear whether grey literature sources were searched. DCV + ASV regimen was not included in the literature search
A3.2	*Have all trials involving at least 2 of the treatments in the Synthesis Comparator Set been included?*	No	Phase 2 trials were not included.
A3.3	*Have all trials reporting relevant outcomes been included?*	No	Phase 2 trials were not included.
A3.4	*Have additional trials been included? If so, is this adequately justified?*	Yes	Trial AI447-031 DCV + ASV versus TEL + PR, which was not identified in the literature search, was included in the analysis
A4 Treatment definition			
A4.1	*Are all the treatment options restricted to specific doses and co-treatments, or have different doses and co-treatments been "lumped" together? If the latter, is it adequately justified?*	*Partial*	The model analyzed each regimen for the DAAs as separate nodes. It appears that different treatment durations were pooled together. It was not justified why the model did not analyze each dosing regimen for the DAAs as separate nodes.
A4.2	*Are there any additional modelling assumptions?*	*Yes*	No additional modelling assumptions were made.
A5 Trial outcomes and scale of measurement chosen for the synthesis			
A5.1	*Where alternative outcomes are available, has the choice of outcome measure used in the synthesis been justified?*	*Yes*	SVR is an appropriate outcome to assess efficacy in CHC trials.
A5.2	*Have the assumptions behind the choice of scale been justified?*	*No*	Data are reported as OR, which may be misinterpreted as a risk ratio (RR) and could appear to inflate the treatment effect.
A6 Patient population: trials with patients outside the target population			

Table		Item Satisfactory?	Comments
A6.1	*Do some trials include patients outside the target population? If so, is this adequately justified?*	*Partial*	The authors included studies that enrolled patients with other genotypes if limited to a small proportion of the total population.
A6.2	*What assumptions are made about the impact, or lack of impact, this may have on the relative treatment effects? Are they adequately justified?*	*Yes*	Most studies included patients with genotype 1. Few studies included patients with other genotypes; however, only data for genotype 1b were used in the analyses.
A6.3	*Has an adjustment been made to account for these differences? If so, comment on the adequacy of the evidence presented in support of this adjustment, and on the need for a sensitivity analysis.*	*Yes*	No adjustments were needed.
A7 Patient population: heterogeneity within the target population			
A7.1	*Has there been a review of the literature concerning potential modifiers of treatment effect?*	*No*	Fibrosis severity, presence of Q80K polymorphism and IL28B genotype, are considered clinically important effect modifiers for different therapies.
A7.2	*Are there apparent or potential differences between trials in their patient populations, albeit within the target population? If so, has this been adequately taken into account?*	*No*	Treatment groups varied in the proportion with factors associated with poorer treatment response, including cirrhosis, and IL28B CC genotype. These factors were not adjusted for in the analyses and no sensitivity or subgroup analyses were conducted.
A8 Risk of bias			
A8.1	*Is there a discussion of the biases to which these trials, or this ensemble of trials, are vulnerable?*	*No*	The authors did not assess each study's risk of bias related to selection, performance, detection, attrition, reporting, or other sources of bias.
A8.2	*If a bias risk was identified, was any adjustment made to the analysis and was this adequately justified?*	*No*	No adjustment for risk of bias.
A9. Presentation of the data			
A9.1	*Is there a clear table or diagram showing which data have been included in the base-case analysis?*	*Partial*	The authors present a network diagram and study characteristics, but no raw data tables for the individual trials.
A9.2	*Is there a clear table or diagram showing which data have been excluded and why?*	*No*	
B. METHODS OF ANALYSIS AND PRESENTATION OF RESULTS ***B1 Meta-analytic methods***			
B1.1	*Is the statistical model clearly described?*	*Partial*	Although an explanation of the methods is provided, details on priors, convergence, and number of iterations were not supplied in the text.
B1.2	*Has the software implementation been documented?*	*No*	Statistical software R and OpenBUGS. Codes were not provided
B2. Heterogeneity in the relative treatment effects			
B2.1	*Have numerical estimates been provided of the degree of heterogeneity in the relative treatment effects?*	*No*	The authors did not report the degree of heterogeneity across pairwise comparisons.
B2.2	*Has a justification been given for choice of random- or fixed-effect models? Should sensitivity analyses be considered?*	*No*	No DIC statistics, residual deviance, or between-study variance reported for the various models.
B2.3	*Has there been adequate response to heterogeneity?*	*No*	Potential heterogeneity largely ignored, where Japanese studies using lower doses than that recommended in Canada were included in the analyses.
B2.4	*Does the extent of unexplained variation in relative treatment effects threaten the*	*No*	Unable to assess.

Table		Item Satisfactory?	Comments
	robustness of conclusions?		
B2.5	*Has the statistical heterogeneity between baseline arms been discussed?*	*No*	No data on baseline rate for the PR treatment arms were provided, and it appears that no examination of the similarity of baseline rates across trials was conducted.
B3 Baseline model for trial outcomes			
B3.1	*Are baseline effects and relative effects estimated in the same model? If so, has this been justified?*		NA
B3.2	*Has the choice of studies to inform the baseline model been explained?*		NA
B4 Presentation of results of analyses of trial data			
B4.1	*Are the relative treatment effects (relative to a placebo or "standard" comparator) tabulated, alongside measures of between-study heterogeneity if a RE model is used?*	*No*	Relative treatment effects (relative to a placebo or "standard" comparator) were not tabulated alongside measures of between-study heterogeneity.
B4.2	*Are the absolute effects on each treatment, as they are used in the CEA, reported?*	*No*	Relative OR and rate difference and 95% CrI are reported only. Data for baseline rates required for CEA are not reported.
C. ISSUES SPECIFIC TO NETWORK SYNTHESIS ***C1 Adequacy of information on model specification and software implementation***			
C2. Multi-arm trials			
C2.1	*If there are multi-arm trials, have the correlations between the relative treatment effects been taken into account?*	*No*	Nothing mentioned about adjustment for correlation.
C3 Connected and disconnected networks			
C3.1	*Is the network of evidence based on randomized trials connected?*	*Yes*	Connected network.
C4 Inconsistency			
C4.1	*How many inconsistencies could there be in the network?*	*No*	There are no closed loops.
C4.2	*Are there any a priori reasons for concern that inconsistency might exist, due to systematic clinical differences between the patients in trials comparing treatments A and B, and the patients in trials comparing treatments A and C, etc.?*	*Partial*	
C4.3	*Have adequate checks for inconsistency been made?*	*No*	It appears that no assessment of inconsistency was conducted.
C4.4	*If inconsistency was detected, what adjustments were made to the analysis, and how was this justified?*	*No*	Inconsistency not assessed.

ASV = asunaprevir; CEA = cost-effectiveness analysis; CHC = chronic hepatitis C; CrI = credible interval; DAA = direct-acting antiviral; DCV = daclatasvir; DIC = deviance information criterion; HCV = hepatitis C virus; NA = not available; OR = odds ratio; PR = pegylated interferon plus ribavirin; RE = relative effects; RR = risk ratio; SVR = sustained virologic response; TEL = telaprevir.

APPENDIX 9: SAMPLE SIZE CALCULATIONS FOR THE INCLUDED STUDIES

TABLE 28: DETAILS OF SAMPLE SIZE CALCULATIONS FOR THE INCLUDED STUDIES

Study	Efficacy	Harms
DUAL	Target sample sizes of 200 (treatment-naive cohort receiving DCV + ASV), 200 (non-responder), and 225 (ineligible, intolerant) patients, the width of the 95% CI for the SVR12 rate would be at most 14%.	Target sample sizes of 200 (treatment-naive cohort receiving DCV + ASV), 200 (non-responder), and 225 (ineligible, intolerant) patients would ensure that safety events occurring at a rate of 1.2% or higher (≥ 1.1% for the ineligible or intolerant cohort) would be detected with at least 90% probability; 100 treatment-naive patients receiving placebo would detect with at least 90% probability safety events occurring at a 2.3% rate.
NIPPON	A target sample size of 120 IFN-ineligible or -intolerant patients and 80 prior non-responder patients provides the following 2-sided 95% CI for observed SVR24 rates: IFN-intolerant 90% (108 of 120) (84% to 96%) 85% (102 of 120) (78% to 92%) 80% (96 of 120) (72% to 88%) Non-responder 90% (72 of 80) (83% to 97%) 85% (68 of 80) (77% to 93%) 80% (64 of 80) (71% to 89%) With 120 IFN-ineligible or -intolerant patients, the study will have greater than 80% power to detect an SVR24 rate greater than 30%, assuming the true SVR24 rate is at least 43%, and with 80 non-responder patients, the study would have greater than 80% power to detect an SVR24 rate greater than 45%, assuming the true SVR24 rate is at least 62%.	A target sample size of approximately 120 IFN-ineligible naive or -intolerant patients, 80 prior non-responders, and a target sample size of 200 in total can detect, with 80% probability, a safety event that occurs at an incident rate of 1.4%, 2.0%, and 0.9%, respectively.
031	A target sample size of 204 IFN-eligible patients (assigned 1:1 to DAA or TEL groups) provided at least 80% power to infer that the DAA group is non-inferior to the TEL group, for the difference (DAA versus TEL) in the proportion of patients with SVR12, at the alpha of 0.025 (one-sided) and a non-inferiority margin of –15%, assuming that the true SVR12 rates were 76% for the DAA group, and 74% for the TEL group.	NR
QUAD	A sample size of 350 genotype 1 CHC patients ensures a 95% CI for SVR12 with a width < 11%.	A target sample size of 390 patients would be able to detect, with 90% probability, a safety event occurring at an incidence of 0.6%.

ASV = asunaprevir; CHC = chronic hepatitis C; CI = confidence interval; DAA = direct-acting antiviral; DCV = daclatasvir; IFN = interferon; NR = not reported; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; TEL = telaprevir.

Source: Manns,[14] Kumada,[15] Jensen,[16] Clinical Study Report.[10-13]

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