Common Drug Review
Clinical Review Report

September 2015

Drug	daclatasvir (Daklinza)
Indication	In combination with other agents for the treatment of chronic hepatitis C (CHC) infection in adults with hepatitis C virus (HCV) genotype 1, and 2 infection and compensated liver disease (including cirrhosis)[a] Notice of Compliance (NOC) with conditions: Use in combination with other agents for the treatment of CHC in adult patients with HCV genotype 3 and compensated liver disease, including cirrhosis.
Listing request	For treatment-naive and treatment-experienced patients (with pegylated interferon plus ribavirin-based therapies) for the following regimen: • Daclatasvir (DCV) plus sofosbuvir (SOF) for genotype 3 CHC
Dosage form(s)	60 mg tablet
NOC date	August 13, 2015
Manufacturer	Bristol-Myers Squibb Canada Inc.

[a] Not approved for treatment-experienced patients with genotype 2 HCV and cirrhosis.

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

TABLE OF CONTENTS

Tables

Figure

ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
ASV	asunaprevir
BOC	boceprevir
BMS	Bristol-Myers Squibb
CHC	chronic hepatitis C
CI	confidence interval
DAA	direct-acting antiviral
DCV	daclatasvir
EQ-5D	EuroQol 5-Dimensions Questionnaire
HCV	hepatitis C virus
IFN	interferon
IPD	individual patient data
ITC	indirect treatment comparison
LLOQ	lower limit of quantification
MAIC	matching-adjusted indirect comparison
mITT	modified intention-to-treat
NMA	Network meta-analysis
PR	pegylated interferon plus ribavirin
RBV	ribavirin
RNA	ribonucleic acid
SIM	simeprevir
SOF	sofosbuvir
SVR	sustained virologic response
TEL	telaprevir

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 they have been infected.[1] There are six major hepatitis C virus (HCV) genotypes; genotype 1 infections are the most common in Canada (approximately 65%).[1] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, respectively.[1] Hepatitis C most commonly affects people over 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) drugs come onto the market. A number of interferon (IFN)-free DAA regimens have recently been approved in Canada for CHC genotypes 1 to 4, with improved tolerability, high response rates, and shorter treatment durations than the previous IFN-based treatment regimens.[8] Daclatasvir (DCV), a DAA agent, is a highly selective inhibitor of the HCV nonstructural protein 5A (NS5A) replication complex. The recommended dose is 60 mg once daily in combination with sofosbuvir (SOF) for genotype 1, 2, or 3 CHC.

Indication
In combination with other agents for the treatment of CHC infection in adults with HCV genotype 1, and 2 infection and compensated liver disease (including cirrhosis)[a] NOC with conditions: Use in combination with other agents for the treatment of CHC in adult patients with HCV genotype 3 and compensated liver disease, including cirrhosis
Listing criteria requested by sponsor
In combination with other agents for the treatment of CHC infection and compensated liver disease (including cirrhosis) for the following regimen: • DCV (as part of a regimen of DCV + SOF (Sovaldi®-Gilead): Treatment of genotype 3 CHC infection

[a] Not approved for treatment-experienced patients with HCV genotype 2 and cirrhosis.

The objective of this systematic review was to evaluate the beneficial and harmful effects of DCV in combination with other drugs for the treatment of CHC genotypes 1 to 4, based on the anticipated indication, prior to Health Canada's approval. This was to include DCV in combination with asunaprevir (ASV); however, due to a delay in the approval of ASV, data related to ASV have been removed from this report.

Results and Interpretation

Included Studies

Two open-label, uncontrolled studies met the inclusion criteria (Study 040, ALLY-3). The patients enrolled had genotype 3 (ALLY-3) or genotype 1, 2, or 3 (040) CHC and included both treatment-naive and treatment-experienced cohorts. DCV was combined with SOF for 12 weeks (ALLY-3, 040) or 24 weeks (040) ± ribavirin (RBV). The sample size per treatment cohort ranged from 14 to 101 patients. Both trials were conducted in the US. The primary outcome was sustained virologic response 12 weeks after the end of treatment (SVR12). Key limitations included the lack of direct head-to-head comparison with alternative therapies. Limited data were available due to the small sample sizes. Of note, despite the scientific limitations associated with uncontrolled study designs, these designs were considered to be sufficient for granting conditional regulatory approval (i.e., NOC with conditions) by Health Canada.

Efficacy

Among patients who received DCV + SOF for 12 or 24 weeks, 86% to 100% of patients with genotype 1, 2, or 3 CHC achieved SVR12 in the ALLY-3 and 040 studies. In treatment-naive and treatment-experienced genotype 3 CHC patients (ALLY-3), the response rate was lower among those with cirrhosis (58% and 69%) than those without cirrhosis (97% and 94%), and all but one of the patients who did not achieve SVR12 failed due to a relapse. In ALLY-3, 9% of treatment-naive and 14% of treatment-experienced genotype 3 patients relapsed. No relapses or on-treatment failures were reported in study 040 among the genotype 1, 2, or 3 patients given DCV + SOF. However, the sample sizes were small per treatment group in the phase 2 study 040 (range 14 to 41); thus, the findings should be interpreted with caution.

[redacted]

Indirect Treatment Comparison

The manufacturer submitted indirect treatment comparisons for DCV + SOF ± RBV in patients with genotype 1 or 3 CHC. Although DCV combinations were found to be comparable or superior to other treatments, the indirect treatment comparison excluded the IFN-free regimens that are the current standard of care for genotype 1 CHC. Moreover, there is currently 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 thus its strengths and weaknesses still require investigation by the research community.

Harms

The incidence of adverse events was high (more than 66%) for all treatment groups, with headache, nausea, and fatigue reported most frequently. The incidence of serious adverse events ranged from 0% to 14% and the proportion of patients who stopped treatment due to adverse events ranged from 0% to 7% per treatment group. DCV therapies compared favourably to 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.

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.

Conclusions

Based on data from two uncontrolled studies, DCV was associated with high rates of SVR12 when combined with SOF in patients with genotype 1, 2, or 3 CHC. The data were limited due to the small numbers of patients treated, in particular, those with genotype 1 or 2 CHC, and those with cirrhosis. No high-quality evidence is available on the comparative efficacy and safety of DCV + SOF versus other DAA regimens or combinations currently in use in Canada due to the lack of head-to-head controlled studies, and due to the limitations of the manufacturer-supplied indirect treatment comparisons. DCV + SOF combination therapy appears to be well tolerated and was not associated with clinically important decreases in quality of life during treatment. However, comparative data are lacking for the current interferon-free regimens that have become the standard of care.

TABLE 1: SUMMARY OF RESULTS

Outcome	ALLY-3 Genotype 3		Study 040 Genotype 2 or 3		Study 040 Genotype 1		
	DCV + SOF 12 Weeks		DCV + SOF 24 Weeks Treatment-Naive	DCV + SOF + RBV 24 Weeks Treatment-Naive	DCV + SOF 12 Weeks Treatment-Naive	DCV + SOF 24 Weeks Treatment-Naive	DCV + SOF 24 Weeks Treatment-Experienced
	Treatment-Naive	Treatment-Experienced					
SVR12							
n/ N	91/101	44/51	14/14	12/14[a]	41/41	14/14	21/21
% (95% CI)	90% (83, 95)	86% (74, 94)	100% (85, 100)[b]	86% (66, 96)[a,b]	100% (95, 100)[b]	100% (85, 100)[b]	100% (90, 100)[b]
Relapse							
n/ N	9/100	7/51	0	0	0	0	0
%	9%	14%	0%	0%	0%	0%	0%
Serious adverse events							
n/N	1/101	0/51	4/28[c]	2/14	1/41	4/28[c]	0/21
%	1%	0%	14%[c]	14%	2%	14%[c]	0%
Discontinued treatment due to adverse event							
n/N	0/101	0/51	1/28[c]	1/14	0/41	1/28[c]	0/21
%	0%	0%	4%[c]	7%	0%	4%[c]	0%

CI = confidence interval; DCV = daclatasvir; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment.

[a] One patient with missing data at week 12 achieved SVR24 (SVR24: 93%; 80% CI, 75% to 99%).

[b] 80% CI.

[c] Data reported includes pooled adverse events for treatment-naive patients with genotype 1, 2, and 3 CHC who received DCV + SOF for 24 weeks.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hepatitis C infection is caused by an enveloped, single-stranded linear ribonucleic acid (RNA) virus of the *Flaviviridae* family. In 2013, an estimated 250,000 Canadians had chronic hepatitis C virus (HCV) infection, but the exact number affected is not known, as 30% to 70% of patients are unaware they have been infected.[1] A total of 11,357 cases of HCV were reported in Canada in 2009, mostly due to injection drug use.[2] Hepatitis C most commonly affects people over 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 people.[2] There are six major HCV genotypes, of which genotype 1 infections are the most common in Canada (65%).[1] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, respectively.[1]

Of those infected, approximately 25% clear infection spontaneously (range 15% to 45%) and the remainder develop chronic infection.[9-11] 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 co-infection, obesity, and increasing age are associated with an increased risk of liver disease progression.[3,12] 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 burdens. 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 chronic hepatitis C (CHC) infection continues to evolve rapidly. Prior to 2011, pegylated interferon plus ribavirin (PR) was the gold standard therapy for patients with CHC infection. Approximately half of patients infected with genotype 1 HCV could expect to achieve sustained virologic response (SVR) with a 48-week course of PR therapy.[8] In recent years, greater understanding of the HCV replication cycle has resulted in the development of direct-acting antiviral (DAA) agents that target several types of the 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, telaprevir [TEL], simeprevir, and sofosbuvir [SOF]), were used in combination with PR in patients with genotype 1 CHC (Table 5). A major limitation of PR-based treatment regimens has been their tolerability. A number of interferon (IFN)-free DAA regimens have now been approved in Canada for HCV genotype 1, 2, 3, and 4 that have improved tolerability, high response rates, and shorter treatment durations (Table 4).[8] The treatment paradigm for CHC has been shifting rapidly as new evidence emerges. Use of the protease inhibitors, boceprevir and TEL, has been replaced by newer DAA regimens, and TEL is no longer marketed in Canada.[8]

1.3 Drug

Daclatasvir (DCV), a DAA against the HCV, is a highly selective inhibitor of the HCV nonstructural protein 5A (NS5A) replication complex. The recommended dose is 60 mg once daily in combination with SOF for HCV genotype 1, 2, and 3 (Table 2).

Indication (NOC With Conditions)
In combination with other agents for the treatment of CHC infection in adults with HCV virus genotype 1 and 2 infection and compensated liver disease (including cirrhosis)[a] NOC with conditions: Use in combination with other agents for the treatment of CHC in adult patients with HCV genotype 3 and compensated liver disease, including cirrhosis.
Listing Criteria Requested by Sponsor
In combination with other agents for the treatment of CHC infection and compensated liver disease (including cirrhosis) for the following regimen: • DCV (as part of a regimen of DCV+SOF (Sovaldi®-Gilead): Treatment of genotype 3 chronic HCV infection

CHC = chronic hepatitis C; DCV = daclatasvir; HCV = hepatitis C virus; NOC = notice of compliance; PR = pegylated interferon plus ribavirin; SOF = sofosbuvir.
[a] Not approved for treatment-experienced patients with genotype 2 HCV and cirrhosis.

TABLE 2: DACLATASVIR DOSING BY HEPATITIS C VIRUS GENOTYPE

Population	Regimen	Duration
Genotype 1 Treatment-naive[a] or treatment-experienced[b] without cirrhosis	DCV 60 mg daily + SOF 400 mg daily	12 weeks
Genotype 1 Treatment-naive[a] or treatment-experienced[b] with compensated cirrhosis	DCV 60 mg daily + SOF 400 mg daily	24 weeks
Genotype 2[c, d] Treatment-naive[a] with or without compensated cirrhosis	DCV 60 mg daily + SOF 400 mg daily	24 weeks
Genotype 2[c, d] treatment-experienced[b] without compensated cirrhosis	DCV 60 mg daily + SOF 400 mg daily	24 weeks
Genotype 3[c] Treatment-naive[a] or treatment-experienced[b] without cirrhosis	DCV 60 mg daily + SOF 400 mg daily	12 weeks
Genotype 3[c, d] Treatment-naive[a] or treatment-experienced[b] with compensated cirrhosis	DCV 60 mg daily + SOF 400 mg daily	24 weeks

DCV = daclatasvir; HCV = hepatitis C virus; SOF = sofosbuvir.
[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. DCV + SOF is also recommended for HCV genotype 1 patients who failed prior HCV protease inhibitor treatment.
[c] For treatment of HCV genotype 2 and 3 infection, DCV + SOF has been studied only in treatment-naive patients with an assigned treatment duration of 24 weeks. Clinical trial experience with the DCV + SOF regimen in HCV genotype 2 and 3 infection in treatment-naive patients is extrapolated to treatment-experienced-patients.
[d] Addition of ribavirin to the DCV + SOF regimen can be considered for patients with compensated cirrhosis.
Source: Daklinza Draft Product Monograph.[13]

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
Boceprevir	HCV NS3/4A protease inhibitor: The NS3/4A protease is essential for viral replication.	Treatment of genotype 1 CHC infection, in combination with PR, in adult patients (18 years or older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous therapy.	Fatigue, anemia, nausea, headache, dysgeusia
Telaprevir	HCV NS3/4A protease inhibitor: The protease is essential for viral replication.	Treatment of genotype 1 CHC infection, in combination with PR, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.	Rash, pruritus, anemia, nausea, diarrhea, hemorrhoids, anorectal discomfort, dysgeusia, fatigue, vomiting
Simeprevir	HCV NS3/4A protease inhibitor: The protease is essential for viral replication.	Treatment of genotype 1 CHC infection, in combination with PR in adults with compensated liver disease, including cirrhosis. **Conditional marketing authorization** Treatment of CHC genotype 1 use in combination with sofosbuvir in adults with compensated liver disease, (conditional pending the results of studies to verify its clinical benefit).	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
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

Drug	Mechanism of Action	Health Canada Indication	Serious Side Effects/Safety Issues
Ombitasvir/ paritaprevir/ ritonavir and dasabuvir ± ribavirin	Ombitasvir: HCV NS5A inhibitor, which inhibits viral replication. Paritaprevir: HCV NS3/4A protease inhibitor, which inhibits viral replication. Dasabuvir: non-nucleoside polymerase inhibitor encoded by the NS5B gene, which is essential for replication of the viral genome. Ritonavir: pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir. It is not active against HCV.	Treatment of adults with genotype 1 chronic HCV infection, including those with compensated cirrhosis.	Fatigue, headache, nausea, pruritus, and insomnia
Daclatasvir	Inhibitor of the NS5A replication complex.	In combination with sofosbuvir for the treatment of CHC in adult patients with HCV genotype 1, 2, or 3, infection and compensated liver disease, including cirrhosis.	Headache and fatigue

CHC = chronic hepatitis C; HCV = hepatitis C virus; PR = pegylated interferon plus ribavirin; RNA = ribonucleic acid.
Source: Product monographs.[13-19]

TABLE 4: RECOMMENDED DOSING FOR INTERFERON-FREE DIRECT-ACTING ANTIVIRAL REGIMENS

HCV	Simeprevir/ Sofosbuvir	Sofosbuvir/ Ribavirin	Sofosbuvir/ Ledipasvir	Ombitasvir/Paritaprevir/ Ritonavir and Dasabuvir	Daclatasvir/Sofosbuvir
Genotype 1	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	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	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)	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 patients with genotype 1a infection with cirrhosis who had a previous null response to PR)	Daclatasvir 60 mg tablet daily plus sofosbuvir 400 mg tablet daily (treatment-naive, or treatment-experienced)[a] **Without cirrhosis** 12 weeks **With cirrhosis** 24 weeks
Genotype 2		Sofosbuvir 400 mg tablet once daily in combination with ribavirin for 12 weeks			Daclatasvir 60 mg tablet daily plus sofosbuvir 400 mg tablet daily for 24 weeks (treatment-naive with or without compensated cirrhosis, or treatment-experienced without compensated cirrhosis)[a] Ribavirin may be added in patients with cirrhosis

HCV	Simeprevir/ Sofosbuvir	Sofosbuvir/ Ribavirin	Sofosbuvir/ Ledipasvir	Ombitasvir/Paritaprevir/ Ritonavir and Dasabuvir	Daclatasvir/Sofosbuvir
Genotype 3		Sofosbuvir 400 mg tablet once daily in combination with ribavirin for 24 weeks			Daclatasvir 60 mg tablet daily plus sofosbuvir 400 mg tablet daily (treatment-naive, or treatment-experienced)[a] **Without cirrhosis** 12 weeks **With cirrhosis** 24 weeks Ribavirin may be added in patients with cirrhosis

CHC = chronic hepatitis C virus; HCV = hepatitis C virus; PR = pegylated interferon plus ribavirin; RNA = ribonucleic acid.
[a] Daclatasvir dose should be reduced to 30 mg once daily when co-administered with strong inhibitors of CYP3A4. 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.
Source: Product monographs.[13,16-19]

TABLE 5: DOSING REGIMENS FOR DIRECT-ACTING ANTIVIRALS USED IN COMBINATION WITH PEGYLATED INTERFERON AND RIBAVIRIN

HCV	Boceprevir	Telaprevir	Simeprevir	Sofosbuvir
Genotype 1	Boceprevir 800 mg (four 200 mg capsules) three times daily with PR **Treatment-naive** PR therapy for 4 weeks, triple therapy for 24 weeks, PR therapy for a possible additional 20 weeks based on RGT **Treatment-experienced** PR therapy for 4 weeks and either triple therapy for 32 weeks or triple therapy for 32 weeks plus PR for an additional 12 weeks, based on RGT (prior relapse and prior partial responders) or triple therapy for 44 weeks (prior null responders) **Cirrhotic patients** PR therapy for 4 weeks and triple therapy for 44 weeks	Telaprevir 1,125 mg (three 375 mg tablets) twice daily in combination with PR **Treatment-naive** Triple therapy for 12 weeks, PR therapy for additional 12 or 36 weeks based on RGT **Treatment-experienced** Triple therapy for 12 weeks, PR for additional 12 or 36 weeks based on RGT (prior relapsers), or triple therapy for 12 weeks, PR for additional 36 weeks (prior partial and null responders) **Cirrhotic patients** Triple therapy for 12 weeks, PR for additional 36 weeks	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
Genotype 4				400 mg tablet once daily with PR for 12 weeks

CHC = chronic hepatitis C; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; PR = pegylated interferon plus ribavirin; RGT = response-guided therapy.
Source: Product monographs.[14,15,17,18]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of DCV in combination with other drugs for the treatment of CHC genotypes 1 to 4. This objective was based on the anticipated Health Canada–approved indication for DCV and asunaprevir (ASV). However, due to a delay in the approval of ASV, data related to ASV has been removed from this report.

2.2 Methods

All manufacturer-provided trials considered pivotal in the manufacturer's submission[20] and the draft product monograph[13] 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 genotype 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 co-infection • hepatitis B co-infection • genotype subtype 1a or 1b • renal insufficiency • liver transplant • decompensated liver disease
Intervention	Daclatasvir 60 mg daily in combination with: • asunaprevir 100 mg twice daily (genotype 1b) • sofosbuvir 400 mg daily (genotype 1, 2, 3) • asunaprevir 100 mg twice daily plus PR (genotype 1, 4)
Comparators	Genotype 1: • ledipasvir/sofosbuvir • ombitasvir/paritaprevir/ritonavir and 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/no treatment Genotype 2, 3: • sofosbuvir in combination with ribavirin • placebo in combination with PR • placebo/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 agent; 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.

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

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

The initial search was completed on March 17, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on July 15, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), and Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

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

3. RESULTS

3.1 Findings From the Literature

A total of six studies were identified from the literature for inclusion in the systematic review (Figure 1). Two studies evaluated DCV + SOF and have been summarized in this report.[21,22] Four additional studies of DCV combined with ASV have not been reported (DUAL, NIPPON, QUAD, 031).[23-26] The included studies for DCV + SOF are summarized in Table 7, and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

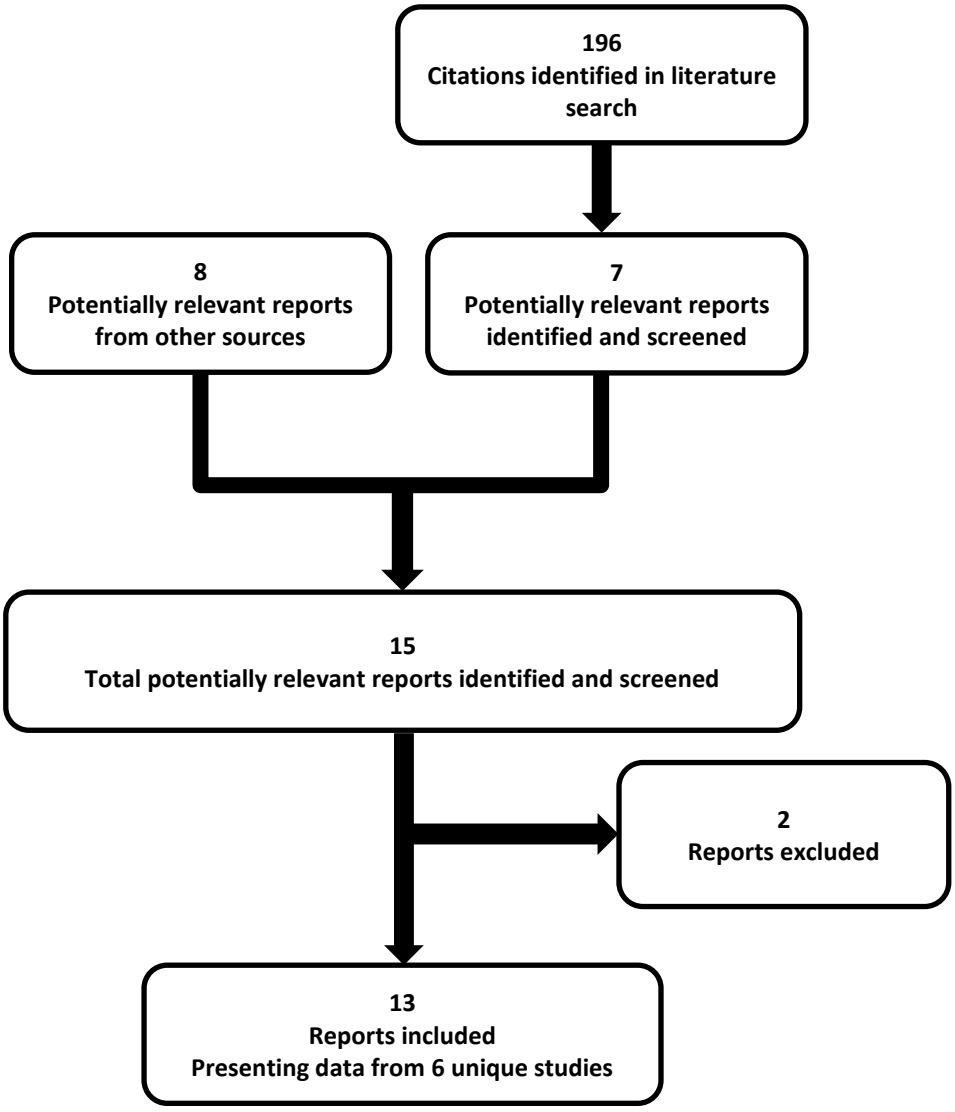


TABLE 7: DETAILS OF INCLUDED STUDIES — DACLATASVIR PLUS SOFOSBUVIR

		AI444-040 (Pivotal)	ALLY-3 AI444-218 (Pivotal)
DESIGNS & POPULATIONS	**Study Design**	OL RCT (4 separate randomizations)	Non-randomized, OL 2 cohorts
	Locations	US	US
	Enrolled (N)	211	152
	Inclusion Criteria	• Adults with CHC who were 18 to 70 years of age and were either: • treatment-naive with genotype 1, 2, or 3 CHC or • non-responders to BOC or TEL + PR with genotype 1 CHC.	• Genotype 3 CHC aged ≥ 18 years who were either: • treatment-naive (cohort 1) or • treatment-experienced (cohort 2).[a]
	Exclusion Criteria	• Co-infection with HIV or hepatitis B • Discontinued TEL or BOC due to adverse events • Cirrhosis • Decompensated liver disease • Cancer • Recent substance abuse • Contraindication to PR • CrCl < 60 mL/min	• Co-infection with HIV or hepatitis B or mixed HCV infections • Mepatic decompensation • HCC or other cancer • Intolerant to NS5A inhibitors or SOF + RBV (adverse events other than anemia) • Active substance abuse • Severe psychiatric disorder • Prior organ transplant • CrCl < 50 mL/min
DRUGS	**Intervention**	Treatment-naive G1, G2, G3: • SOF 400 mg/d × 1 week then SOF 400 mg + DCV 60 mg/d × 23 weeks • SOF 400 mg + DCV 60 mg/d × 24 weeks or • SOF 400 mg + DCV 60 mg/d + RBV (G1: 1,000 to 1,200 mg/d; G2, G3: 800 mg/d) × 24 weeks Treatment-naive G1: • SOF 400 mg + DCV 60 mg/d × 12 weeks or • SOF 400 mg + DCV 60 mg/d + RBV 1,000 to 1,200 mg/d × 12 weeks Treatment-experienced G1: • SOF 400 mg + DCV 60 mg/d × 24 weeks or • SOF 400 mg + DCV 60 mg/d + RBV 1,000 to 1,200 mg/d × 24 weeks	• SOF 400 mg + DCV 60 mg/d × 12 weeks
	Comparator(s)	None	None
DURATION	**Phase**	2	3
	Open-label	12 to 24 weeks	12 weeks
	Follow-up	48 weeks	24 weeks

		AI444-040 (Pivotal)	ALLY-3 AI444-218 (Pivotal)
OUTCOMES	**Primary end point**	SVR12	SVR12
	Other end points	• SVR24 • relapse • harms	• relapse • harms • EQ-5D
NOTES	**Publications**	Sulkowski[21]	Nelson[22]

ASV = asunaprevir; BOC = boceprevir; CHC = chronic hepatitis C; CrCl = creatinine clearance; d = day; DAA = direct-acting antiviral agent; DCV = daclatasvir; EQ-5D = EuroQol 5-dimensions questionnaire; G = genotype; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; OL = open-label; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RCT = randomized controlled trial; RNA = ribonucleic acid; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; TEL = telaprevir.

[a] Prior treatment with interferon alfa (with or without RBV), SOF + RBV, or other anti-HCV agents (e.g., cyclophilin inhibitors and inhibitors of microRNA).

Source: Sulkowski,[21] Nelson,[22] Clinical Study Reports.[27,28]

Note: One additional report was included (CDR submission for Daklinza[20]). Four studies[23-26,29-31] and one additional report[32] that evaluated DCV + ASV dosing regimens were not summarized as part of this report.

3.2 Included Studies

3.2.1 Description of studies

Two pivotal trials met the inclusion criteria and have been summarized in this report (ALLY-3, 040) (Table 7). The primary outcome in both trials was sustained virologic response 12 weeks after the end of treatment (SVR12).

These two open-label trials (040, ALLY-3) evaluated DCV with SOF in patients with genotype 1, 2, or 3 CHC.

- Study 040 conducted four separate randomizations of different patient populations. Patients with CHC genotype 1 (treatment-naive; non-responder to boceprevir or TEL plus PR), and CHC genotype 2, or 3 (treatment-naive) were randomized to different DCV + SOF 12 or 24 weeks ± ribavirin (RBV) regimens. Randomization of genotype 1 patients was stratified by genotype subtype (1a/1b) and randomization of patients with genotype 2 or 3 was stratified by genotype.
- ALLY-3 was a non-randomized study that enrolled a treatment-naive and a treatment-experienced cohort of patients with CHC genotype 3. All patients received DCV + SOF for 12 weeks.

Study 040 included additional cohorts that did not meet this review's inclusion criteria and these groups have not been summarized in this report. In study 040, patients who received treatment regimens that were not consistent with the product monograph (SOF × 1 week then DCV + SOF × 23 weeks, or DCV + SOF + RBV) were excluded.

3.2.2 Populations

a) Inclusion and exclusion criteria

The trials enrolled adults with CHC genotype 3 (ALLY-3) or genotype 1, 2, or 3 (040). Both trials enrolled patients who were treatment-naive and treatment-experienced. In study 040, treatment-experienced patients who were non-responsive to boceprevir or TEL plus PR were enrolled. The majority of treatment-experienced patients in ALLY-3 had received an interferon-based therapy or SOF + RBV.

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

b) Baseline characteristics

Across the studies, the median age ranged from 50 to 59 years, and the proportion of males ranged from 36% to 64% (Table 8). The proportion of patients with cirrhosis (or Metavir fibrosis stage F4) varied from 7% to 25%. In ALLY-3, there were more patients with cirrhosis in the treatment-experienced (25%) than in the treatment-naive (19%) cohort. As ALLY-3 was non-randomized, differences between treatment groups within the trial is expected.

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS

	ALLY-3		Study 040				
	DCV + SOF 12 Weeks		DCV + SOF +RBV	DCV + SOF			
			24 Weeks	24 Weeks	12 Weeks	24 Weeks	24 Weeks
	Treatment-Naive Genotype 3	Treatment-Experienced Genotype 3	Treatment-Naive Genotype 2, 3	Treatment-Naive Genotype 2, 3	Treatment-Naive Genotype 1	Treatment-Naive Genotype 1	Treatment-Experienced Genotype 1
N	101	51	14	14	41	14	21
Age (years), median (range)	53 (24 to 67)	58 (40 to 73)	52 (24 to 66)	50 (31 to 67)	55 (23 to 68)	54 (34 to 62)	59 (26 to 70)
Male, n (%)	58 (57)	32 (63)	5 (36)	6 (43)	20 (49)	9 (64)	13 (62)
HCV Genotype, n (%)							
Genotype 1a					34 (83)	10 (71)	16 (76)
Genotype 1b					7 (17)	4 (29)	5 (24)
Genotype 2			9 (64)	8 (57)			
Genotype 3	101 (100)	51 (100)	5 (36)	6 (43)			
Genotype 4							
Cirrhosis or Metavir F4, n (%)	19 (19)	13 (25)	2 (14)	1 (7)	6 (15)	1 (7)	3 (14)
Baseline HCV RNA, log_{10} IU/mL, mean (SD)	[redacted]	[redacted]	6.6 (0.6)	6.8 (0.5)	6.2 (0.5)	6.6 (0.3)	6.3 (0.4)
Previous response to HCV treatment (%)	NA		NA	NA	NA	NA	
Relapse/ breakthrough		31 (61)					17 (81)
Partial response		2 (4)					5 (24)[a]
Null response		7 (14)					
Other		11 (22)					
Prior HCV treatment (%)	NA		NA	NA	NA	NA	
IFN regimens		[redacted]					
DAA regimen		[redacted]					21 (100)
Other		[redacted]					

BOC = boceprevir; DAA = direct-acting antiviral agent; DCV = daclatasvir; HCV = hepatitis C virus; IFN = interferon; NA = not applicable; RBV = ribavirin; RNA = ribonucleic acid; SD = standard deviation; SOF = sofosbuvir; TEL = telaprevir.

[a] Non-responder was defined as detectable HCV RNA at the end of treatment with a regimen that included either TEL or BOC when dosed in combination with pegylated interferon and ribavirin.

Source: Nelson,[22] Sulkowski,[21] Clinical Study Report.[27,28]

3.2.3 Interventions

Table 9 provides a listing of the treatment regimens administered by study population. In all trials, the dose of DCV was 60 mg daily combined with SOF 400 mg daily (12 or 24 weeks, or 24 weeks plus RBV 800 mg per day). In study 040, those who met predefined futility criteria were eligible to receive rescue therapy (PR) for 24 to 48 weeks.

TABLE 9: DACLATASVIR TREATMENT REGIMEN BY POPULATION AND STUDY

Genotype/Prior Treatment Exposure	Treatment Regimen[a]		
	DCV + SOF 12 Weeks[b]	DCV + SOF 24 Weeks[c]	DCV + SOF +RBV[d] 24 Weeks
Treatment-naive			
1	040	040	
2		040	040
3	ALLY-3	040	040
Treatment-experienced[e]			
1		040	
2			
3	ALLY-3		

CHC = chronic hepatitis C; DCV = daclatasvir; HCV = hepatitis C virus; RBV = ribavirin; SOF = sofosbuvir.
[a] Shaded cells indicate Health Canada–approved dosage regimen. If blank, then no clinical trial data were available for that population and treatment combination.
[b] Twelve-week regimen approved for patients with CHC genotype 1 or 3 without cirrhosis (treatment-naive, treatment-experienced, or interferon-intolerant or ineligible patients).
[c] Regimen of 24 weeks approved for patients with CHC genotype 1 or 3 with cirrhosis (treatment-naive, treatment-experienced, or interferon-intolerant or ineligible patients); treatment-naive genotype 2 patients with or without cirrhosis and treatment-experienced genotype 2 patients without cirrhosis.
[d] Health Canada states that the addition of RBV to the DCV + SOF 24-week regimen may be considered for CHC genotype 2 or 3 patients with compensated cirrhosis.
[e] Health Canada defined treatment-experienced as those who failed prior therapy with an interferon-based regimen, including null or partial response. For patients with CHC genotype 1, DCV + SOF was also recommended for patients who failed prior HCV protease inhibitor treatment.

3.2.4 Outcomes

In both studies, the primary outcome was SVR12. 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.

Relapse was 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 (ALLY-3) or following an HCV RNA level below the LLOQ at the end of treatment (study 040). The relapse rate was calculated using the number of patients who achieved undetectable HCV RNA levels at the end of treatment as 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.

[redacted]

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; was an important medical event that may not have required hospitalization but may have jeopardized the patient; or required intervention.

In study 040, a composite of rash-related adverse events was reported based on a predefined list of Medical Dictionary for Regulatory Activities preferred terms.

3.2.5 Statistical analysis

In the ALLY-3 study, two-sided 95% confidence intervals (CIs) for SVR rates were computed using normal approximations to the binomial distribution, and in study 040 exact binomial two-sided 80% CIs were calculated. Those with missing data were classified as having no response at that visit. In study 040, those who required rescue therapy were classified as non-responders. No between-group statistical comparisons were conducted in study 040 or ALLY-3. Sample size calculations are listed in Appendix 7.

[redacted]

a) Analysis populations

In all trials, the efficacy and safety analyses were based on a modified intention-to-treat (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. Study 040 analyzed patients as treated (i.e., two patients received the wrong treatment and were analyzed based on the treatment received).

The safety data excludes any adverse events that occurred after patients started rescue treatment in study 040.

3.3 Patient Disposition

In the ALLY-3 trial, 12% of patients enrolled in the study did not enter the treatment phase; the most common reason stated was the patient no longer met the inclusion criteria (Table 10). In study 040, 39% of those screened were not randomized. The proportion of patients who did not complete therapy ranged from 0% to 14%.

TABLE 10: PATIENT DISPOSITION

	ALLY-3 Genotype 3		Study 040 Genotype 1, 2, 3				
	DCV + SOF 12 Weeks		DCV + SOF + RBV 24 Weeks	DCV + SOF 24 Weeks	DCV + SOF 12 Weeks	DCV + SOF 24 Weeks	DCV + SOF 24 Weeks
	Treatment-Naive	Treatment-Experienced	Treatment-Naive Genotype 2 or 3	Treatment-Naive Genotype 2 or 3	Treatment-Naive Genotype 1	Treatment-Naive Genotype 1	Treatment-Experienced Genotype 1
Screened, N	NR		350[a]				
Randomized/enrolled, N (%)	[redacted]		14	16[c]	41	14	21
Enrolled and treated, N (%)	152 ([redacted])		14	14	41	14	21
	101	51					
Discontinued, N (%)	1 (1)	0	2 (14)	0	0	1 (7)	0
Adverse event	0	0	1 (7)	0	0	1 (7)	0
Lost to follow-up	0	0	1 (7)	0	0	0	0
Pregnancy	1 (1)	0	0	0	0	0	0
mITT, N	101	51	14	14	41	14	21
Safety, N	101	51	14	14	41	14	21

DCV = daclatasvir; mITT = modified intention to treat; NR = not reported; SOF = sofosbuvir.

[a] Of the 350 patients enrolled in the study, 139 (39%) were not randomized (no longer met study criteria [n = 98], withdrew consent [13], administrative reason [12], other [16]). A total of 107 patients enrolled in treatment groups who received a DCV treatment regimen that did not meet the inclusion criteria for this review are not included in this report. [redacted]

[c] Two patients who were randomized to DCV + SOF × 24 weeks received a different regimen (1 week SOF then 23 weeks SOF/DCV) and were analyzed as treated.

Source: Sulkowski,[21] Nelson,[22] Clinical Study Report.[27,28]

3.4 Exposure to Study Treatments

In the ALLY-3 trial, the median duration of DCV and SOF therapy was 12.0 weeks for both DCV and SOF. The median treatment duration was not reported for study 040; however, one genotype 1 patient in the DCV + SOF for 24 weeks treatment group and two genotype 2/3 patients in the DCV + SOF + RBV for 24 weeks treatment group were reported to have discontinued therapy early.

3.5 Critical Appraisal

3.5.1 Internal validity

Study 040 randomized patients to treatment groups using appropriate methods and allocation concealment (computer-generated randomization sequence and an interactive voice or web response system). The other included study was a non-randomized trial (ALLY-3). Since both trials were uncontrolled, the efficacy of DCV therapy compared with existing treatments cannot be established directly from the studies. Although there are scientific limitations to uncontrolled trials, such study designs are accepted by regulatory bodies for DAA agents in hepatitis C.

Both trials were open-label. 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 ledipasvir plus SOF (0% to 4.1%) or ombitasvir/ paritaprevir/ritonavir and dasabuvir ± RBV (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.

The phase 2 study 040 reported SVR rates with an 80% confidence interval, which will provide narrower intervals that appear more precise than the standard 95% CIs.

Due to the small number of patients enrolled in the treatment groups (range 14 to 101, median 21), efficacy data were limited in patients with genotype 1 and 2 CHC and treatment-experienced patients with genotype 3 CHC. Additionally, limited data were available from study 040 and ALLY-3 on patients who had failed prior DAA treatment, or those with cirrhosis. The findings from these cohorts should be interpreted with caution.

3.5.2 External validity

A considerable proportion of patients were screened for the trials but did not enter the treatment phase. Detailed reasons for exclusion were not reported. 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 co-infection, 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.

Neither 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 (section 2.2, Table 6) are reported subsequently. See Appendix 4 for detailed efficacy data.

3.6.1 Sustained virologic response

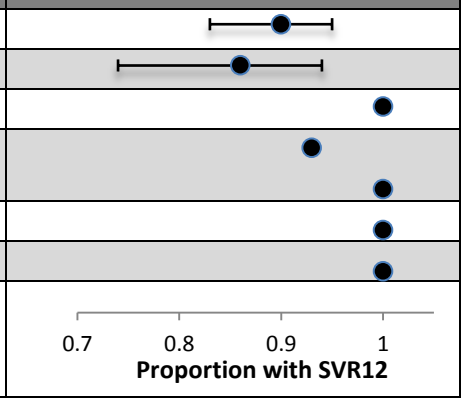
a) DCV + SOF

In the ALLY-3 trial, 90% (95% CI, 83% to 95%) and 86% (74% to 94%) of treatment-naive and treatment-experienced genotype 3 CHC patients, respectively, achieved SVR12 after 12 weeks of DCV + SOF therapy (Table 11). In this trial, patients with cirrhosis had a lower SVR12 rate (58% to 69%, total N = 29) than those without cirrhosis (94% to 97%, total N = 109) (Appendix 4, Table 14). SVR12 rates were similar among patients with prior relapse or partial or null response to treatment, although the number of patients per subgroup was small.

In the phase 2 study 040, 100% of genotype 1 to 3 CHC patients who received DCV + SOF for 12 to 24 weeks achieved SVR12. This included 21 patients who previously failed TEL or boceprevir plus PR therapy. Among the 14 genotype 2 or 3 patients who received DCV + SOF plus RBV for 24 weeks, 93% achieved SVR24 (Table 11, and Appendix 4, Table 13 and Table 14). Of note, the number of patients per treatment group was small (range 14 to 41). No subgroup data were reported in study 040 for the treatment groups of interest in this review.

TABLE 11: PROPORTION OF CHRONIC HEPATITIS C GENOTYPE 1, 2, OR 3 PATIENTS WHO ACHIEVED SVR12 (STUDY 040, ALLY-3)

Study	Population	Treatment	% SVR12 (95% CI)	
ALLY3	G3 naive	DCV + SOF 12 weeks	90% (83 to 95%)	
	G3 experienced	DCV + SOF 12 weeks	86% (74 to 94%)	
040	G2, G3 naive	DCV + SOF 24 weeks	100% (NR)[a,b]	
	G2, G3 naive	DCV + SOF + RBV 24 weeks	93% (NR)[a,b,c]	
	G1 naive	DCV + SOF 12 weeks	100% (NR)[a,d]	
	G1 naive	DCV + SOF 24 weeks	100% (NR)[a,b]	
	G1 experienced	DCV + SOF 24 weeks	100% (NR)[a,e]	



CI = confidence interval; DCV = daclatasvir; G1 = genotype 1; G2 = genotype 2; G3 = genotype 3; NR = not reported; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after the end of treatment.
[a] Ninety-five per cent CIs were not reported but 80% CIs are available in Appendix 4, Table 13, and Table 14.
[b] Sample size = 14 patients.
[c] Data reported is SVR24. One patient with missing data at week 12 achieved SVR 24 weeks after the end of treatment.
[d] Sample size = 41 patients.
[e] Sample size = 21 patients.

3.6.2 Relapse and on-treatment failure

a) DCV + SOF

In the ALLY-3 study, relapse was reported in 9% of treatment-naive and 14% of treatment-experienced genotype 3 CHC patients who received DCV + SOF for 12 weeks. On-treatment failure occurred in 1% of treatment-naive and no treatment-experienced patients.

In study 040, none of the genotype 1, 2, or 3 patients who received DCV + SOF for 12 or 24 weeks or DCV + SOF + RBV for 24 weeks experienced a relapse or had an on-treatment failure (Appendix 4, Table 13 and Table 14).

3.6.3 Quality of life

[redacted]

[redacted]

3.7 Harms

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

3.7.1 Adverse events

The proportion of patients who reported adverse events ranged from 66% to 93% among those who received DCV + SOF (Table 12).

3.7.2 Serious adverse events

Serious adverse events were reported by 0% to 14% of patients who received DCV therapy (Table 12). The incidence was highest among the treatment-naive cohorts that received 24 weeks of DCV + SOF, but these percentages should be interpreted with caution considering the small number of patients enrolled.

3.7.3 Withdrawals due to adverse events

Few patients treated with DCV discontinued therapy due to adverse events (0% to 7%) (Table 12).

3.7.4 Mortality

No deaths were reported in the included studies (Table 12).

3.7.5 Notable harms

During the treatment period, the most frequently reported adverse events among patients who received DCV were headache (20% to 34%), nausea (0% to 36%), and fatigue (14% to 50%) (Table 12). Reported rates of fatigue were higher in treatment groups that received 24 weeks of DCV + SOF, but this could be susceptible to small numbers of patients enrolled in these groups. Anemia was not reported in any patients who received DCV + SOF, except for one patient who also received RBV.

TABLE 12: HARMS

	ALLY-3		Study 040			
	Treatment-Naive Genotype 3 DCV + SOF 12 Weeks	Treatment-Experienced Genotype 3 DCV + SOF 12 Weeks	Treatment-Naive Genotype 1 DCV + SOF 12 Weeks	Treatment-Naive Genotype 1, 2, 3 DCV + SOF 24 Weeks	Treatment-Naive Genotype 2, 3 DCV + SOF + RBV 24 Weeks	Treatment-Experienced Genotype 1 DCV + SOF 24 Weeks
N	101	51	41	28	14	21
Any AE	[redacted]	[redacted]	38 (93)	26 (93)	11 (79)	16 (76)
SAE	[redacted]	[redacted]	1 (2)	4 (14)	2 (14)	0
Death	[redacted]	[redacted]	0	0	0	0
AE leading to discontinuation of study drug	[redacted]	[redacted]	0	1 (4)	1 (7)	0
Common AE						
Anemia	[redacted]	[redacted]	0	0	1 (7)	0
Fatigue	[redacted]	[redacted]	16 (39)	14 (50)	2 (14)	6 (29)
Rash	[redacted]	[redacted]	2 (5)[a]	0 [a]	0 [a]	1 (5) [a]
Pruritus	[redacted]	[redacted]	1 (2)	1 (4)	2 (14)	1 (5)
Depression	[redacted]	[redacted]	2 (5)	3 (11)	2 (14)	1 (5)
Headache	[redacted]	[redacted]	14 (34)	8 (29)	3 (21)	7 (33)
Neutropenia	[redacted]	[redacted]	NR	NR	NR	NR
Nausea	[redacted]	[redacted]	8 (20)	9 (32)	5 (36)	0
Diarrhea	[redacted]	[redacted]	2 (5)	3 (11)	1 (7)	2 (10)
Asthenia	[redacted]	[redacted]	1 (2)	1 (4)	0	0

AE = adverse event; DCV = daclatasvir; N = number of patients; NR = not reported; RBV = ribavirin; SOF = sofosbuvir.
[a] Composite of rash-related Medical Dictionary for Regulatory Activities terms.
Source: Sulkowski,[21] Nelson,[22] Clinical Study Reports.[27,28]

4. DISCUSSION

4.1 Summary of Available Evidence

Two open-label, uncontrolled studies met the inclusion criteria and are summarized in this report (ALLY-3, 040). The patients enrolled had genotype 3 (ALLY-3) or genotype 1, 2, or 3 (040) CHC and included treatment-naive and treatment-experienced cohorts.

DCV was combined with SOF for 12 weeks (ALLY-3, 040) or 24 weeks (040) ± RBV. The primary outcome was SVR12. Both trials were conducted in the US.

Key limitations included the lack of direct head-to-head comparison with alternative therapies. Limited data were available due to the small sample sizes.

4.1.1 Efficacy

Among patients who received DCV + SOF for 12 or 24 weeks, 86% to 100% of patients with genotype 1, 2, or 3 CHC achieved SVR12. In treatment-naive and treatment-experienced genotype 3 patients in the ALLY-3 study, the response rate was lower among those with cirrhosis (58% and 69%) than those without cirrhosis (97% and 94%), and all but one of the patients who did not achieve SVR12 failed due to a relapse. In ALLY-3, 9% of treatment-naive and 14% of treatment-experienced genotype 3 patients relapsed. No relapses or on-treatment failures were reported in study 040 (N = 104). Of note, Health Canada recommends 24 weeks of therapy for genotype 3 patients with cirrhosis, not the 12-week regimen used in ALLY-3. SVR rates among cirrhotic patients who received the 24-week DCV + SOF regimen is not known, as no data were available for this subgroup in study 040. From the abstract of the ALLY-2 trial, SVR rates were 89% (8/9) and 93% (14/15) after 12 weeks of DCV + SOF therapy in treatment-naive and treatment-experienced patients with genotype 1 to 4 CHC and HIV co-infection.[35] SVR rates were 98% and 100% in non-cirrhotic patients. Abstract data from the ALLY-1 trial reported 83% (50/60) of genotype 1 to 4 patients with cirrhosis achieved SVR after 12 weeks of DCV + SOF + RBV.[36] Further data may be needed to determine the optimal dosage regimen in patients with cirrhosis.

Although the manufacturer is seeking Health Canada approval for DCV + SOF in genotypes 1, 2, and 3, the available data are limited by the small sample size (n ≤ 51) enrolled in study 040 (all cohorts) and ALLY-3 (treatment-experienced cohort). No clinical trial data were available for the DCV + SOF 24-week regimen among treatment-experienced patients with genotype 2 or 3 CHC; Health Canada has extrapolated data from other populations to support these recommended dosing regimens.[13] Moreover, the number of patients with cirrhosis who were enrolled was limited, and cirrhosis appears to be an important effect modifier for patients with genotype 3 receiving DCV + SOF. It is unclear if it affects the efficacy of DCV + SOF in other genotypes. Despite the scientific limitations associated with uncontrolled study designs, these designs were considered sufficient by Health Canada to grant conditional regulatory approval (i.e. NOC with conditions). Of note, Health Canada did not approve the use of DCV + SOF in treatment-experienced genotype 2 patients with cirrhosis.

[redacted] Other trial data assessing interferon-based regimens have shown reductions in quality-of-life scores in interferon-based treatment groups.[37]

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. The manufacturer provided an indirect treatment comparison that found that in treatment-naive patients with genotype 1 CHC, DCV + SOF ± RBV was statistically significantly more effective in achieving SVR than TEL, boceprevir, simeprevir, or SOF + PR (Appendix 6). In patients with genotype 3 CHC, DCV + SOF was associated with rates of SVR12 similar to SOF + RBV in treatment-naive and treatment-experienced patients. The validity of the MAIC methods used in the manufacturer's analyses is uncertain; thus, it is difficult to interpret these findings. Reasons for this uncertainty are described in the critical appraisal of the indirect comparison in Appendix 6. No data were available comparing DCV with interferon-free DAA regimens in either the included studies or the manufacturer-provided indirect treatment comparison. The exclusion of interferon-free regimens in the analysis limits the utility of the indirect comparison. To address these evidence gaps, CADTH is undertaking a Therapeutic Review that will provide estimates of the comparative efficacy of interferon-based treatments and the interferon-free DAA regimens recently approved in Canada.[38]

4.1.2 Harms

In the two trials, the incidence of adverse events was high (> 66%) for all treatment groups, with headache, nausea, and fatigue reported most frequently. The incidence of serious adverse events was ≤ 14% and the proportion of patients who stopped treatment due to adverse events was low (0% to 7%). The manufacturer-provided indirect treatment comparison reported that, for patients with genotype 1 CHC, DCV + SOF ± RBV had statistically significantly lower rates of discontinuation due to adverse events than TEL, boceprevir, or simeprevir plus PR. In trials that assessed ledipasvir plus SOF and ombitasvir/paritaprevir/ritonavir and dasabuvir ± RBV, the withdrawal rates reported (0% to 1.1% and 0% to 1.8%, respectively) were similar to or lower than those reported in some DCV groups.[33,34] However, without a formal comparison, no conclusion can be made based on these observed differences, and multiple factors other than drug therapy in open-label trials could contribute to these differences. It should be noted that higher percentages can be reported in these DCV trials due to the small number of patients enrolled in some groups, but absolute numbers remain small, making it difficult to draw conclusions on the true occurrence of adverse effects in some subpopulations.

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.

5. CONCLUSIONS

Based on data from two uncontrolled studies, DCV was associated with high rates of SVR12 when combined with SOF in patients with genotype 1, 2, or 3 CHC. The data were limited due to the small numbers of patients treated, in particular, those with genotype 1 or 2 CHC, and those with cirrhosis. No high-quality evidence is available on the comparative efficacy and safety of DCV + SOF versus other DAA regimens or combinations currently in use in Canada due to the lack of head-to-head controlled studies, and due to limitations of the manufacturer-supplied indirect treatment comparisons. DCV + SOF combination therapy appears to be well tolerated, and was not associated with clinically important decreases in quality of life during treatment. However, comparative data with the current interferon-free regimens that have become the standard of care are lacking.

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 Groups 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 non-governmental organization whose mandate is to address access to treatment, care, and support for people living with HIV or hepatitis C virus (HCV). Full membership is limited to people 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 regards 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 of, 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 their educational activities.

Three people 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 daclatasvir, 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 co-infected 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 impacts their cognitive functions, affecting their concentration/attention span, speed of thought,

fluency of speech, learning, and memory. 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, with 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 one's mood swings, dietary problems, and lack of energy and concentration, while shouldering the responsibility for managing doctor's appointments, drug regimens, and household responsibilities. As the patient's symptoms and behaviour become more difficult to manage, families and marriages can break apart due to stress, financial difficulties, and social isolation.

The current standard of care is changing; previously, the preferred regimen 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 if the treatments will be successful or if their efforts to complete therapy and endure the side effects will be worth it. Adverse effects of treatment may impact on patients' ability to continue working and to manage their household or child care. 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, and were 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 daclatasvir is that the treatment's high SVR rates, which have been reached in clinical trials when daclatasvir was 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, it is expected that daclatasvir will open up treatment to patients who had contraindications to, or could not tolerate, interferon-based treatments, such as those patients with HIV co-infection, or autoimmune conditions. With a cure, they expect their cirrhosis will reverse and their risk of end-stage liver disease will be reduced. Some may be able to return to work, and everyone's quality of life of will improve.

Patients tend not to differentiate the various new drugs from one another since they are all so much better than the existing ones. The new drugs share the characteristics of being mostly tested on genotype 1, having far greater efficacy, needing a much shorter treatment time, requiring no IFN or needles, having very few side effects, and having an extremely high price tag. They are excited about daclatasvir's diverse uses, given that it has been studied in combination with other new treatments and in patients with cirrhosis, HIV, and liver transplant as well as those who have failed other therapies, and that it has been studied in multiple genotypes. However, some patients were concerned regarding side effects, specifically that RBV might be needed for some HCV sufferers. Several patients noted they have been deterred from seeking treatment because of the continued presence of RBV in contemporary therapy options. Patients also questioned the place of daclatasvir amid contemporary HCV therapies like sofosbuvir and ledipasvir-sofosbuvir (i.e., treatments that include 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's a high probability of a cure, the expectation is that daclatasvir has far fewer adverse side effects than past treatments.

Physicians treating patients with daclatasvir combined with IFN and RBV found their patients still had to deal with IFN-related side effects. Those who treated patients with daclatasvir plus asunaprevir found their patients had a fairly easy time with treatment, with no noticeable side effects, and some patients found 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 stopped collecting disability payments 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 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 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 someone.

4. Additional Information

Patients are concerned that the prices of these drugs will be so high that CADTH (and/or provincial drug plans) will either not approve the treatment at all, or require patients to undergo and fail very challenging standard treatments (with both INF and RBV) before allowing access to daclatasvir. Delaying treatment until liver disease is more advanced impacts patients' physical and mental well-being. It is frustrating for individuals, especially those who are experiencing multiple barriers, to be told 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 CHC 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 time will run out for some patients. One patient indicated there are no other diseases in which a patient has to prove significant damage to his or 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 17, 2015
Alerts:	Weekly search updates until (July 15, 2015)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Daclatasvir* or Daklinza* or daklatasavir* or daklatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or LI2427F9CI or 1009119-64-5).ti,ot,ab,sh,hw,rn,nm. use pmez
2	*daclatasvir/
3	(Daclatasvir* or Daklinza* or daklatasavir* or daklatasvir* or BMS 790052 or BMS790052 or EBP 883 or EBP883 or LI2427F9CI or 1009119-64-5).ti,ab. use oemezd
4	1 or 2 or 3
5	4 not conference abstract.pt.
6	remove duplicates from 5

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	March 2015
Keywords:	Daklinza (daclatasvir)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey Matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Pellicelli AM, Montalbano M, Lionetti R, Durand C, Ferenci P, D'Offizi G, et al. Sofosbuvir plus daclatasvir for post-transplant recurrent hepatitis C: potent antiviral activity but no clinical benefit if treatment is given late. Dig Liver Dis. 2014 Oct;46(10):923-7.	Not a RCT
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 non-pivotal trial

References Excluded After Screening	Reason for Exclusion
Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet. 2014 Nov 1;384(9954):1597-605.	Delay in Health Canada approval for asunaprevir
Clinical Study Report: AI447028. A phase 3 study with Asunaprevir and Daclatasvir (DUAL) for null or partial responders to Peginterferon Alfa and Ribavirin (P/R), intolerant or ineligible to P/R subjects and treatment-naive subjects with chronic hepatitis C genotype 1b infection [CONFIDENTIAL internal manufacturer's report]. Princeton (NJ): Bristol-Myers Squibb Company; 2014 Feb 10.	
Kumada H, Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, et al. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. Hepatology. 2014 Jun;59(6):2083-91.	
Clinical Study Report: AI447026. A phase 3 Japanese study of BMS-790052 plus BMS-650032 combination therapy in chronic hepatitis C genotype 1b infected subjects who are non- Response to Interferon plus Ribavirin and Interferon-based therapy ineligible naive/intolerant [**CONFIDENTIAL** internal manufacturer's report]. Princeton (NJ): Bristol-Myers Squibb Company; 2013 Sep 14.	
Jensen D, Sherman KE, Hezode C, Pol S, Zeuzem S, Ledinghen V, et al. Daclatasvir and asunaprevir plus peginterferon alfa and ribavirin in HCV genotype 1 or 4 non-responders. J Hepatol. 2015 Feb 19.	
Clinical Study Report: AI447029. A phase 3, open-label study with asunaprevir and daclastasvir plus Pegintergeron Alfa-2a (Pegasys) and Ribavirin (Copegus) (P/R) (QUAD) for subjects who are null or partial responders to Peginterferon Alfa 2a or 2b plus Ribavirin with chronic hepatitis C genotypes 1 or 4 infection[**CONFIDENTIAL** internal manufacturer's report]. Princeton (NJ): Bristol-Myers Squibb Company; 2014 Mar 5.	
Clinical Study Report: AI447031. A phase 3, comparative study of Asunaprevir and Daclatasvir (DUAL) combination therapy versus Telaprevir therapy in Japanese genotype 1b chronic hepatitis C IFN eligible-naive subjects with a single arm assessment of DUAL therapy in IFN-therapy relapsers [**CONFIDENTIAL** internal manufacturer's report]. Princeton (NJ): Bristol-Myers Squibb Company; 2014 Apr 9.	
CDR submission: Sunvepra™ (asunaprevir), 100 mg capsule. Company: Bristol-Myers Squibb [**CONFIDENTIAL** manufacturer's submission]. Saint-Laurent (QC): Bristol-Myers Squibb Canada; 2015 Feb.	

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 13: EFFICACY OUTCOMES FOR DACLATASVIR PLUS SOFOSBUVIR IN GENOTYPE 1 CHRONIC HEPATITIS C (STUDY 040)

Outcome	Study 040 Genotype 1					
	Treatment-Naive				Treatment-Experienced (Non-response to BOC or TEL + PR)[a]	
	DCV + SOF 12 Weeks		DCV + SOF 24 Weeks		DCV + SOF 24 Weeks	
	n/N	% (80% CI)	n/N	% (80% CI)	n/N	% (80% CI)
SVR12	41/41	100% (95, 100)	14/14	100% (85, 100)	21/21	100% (90, 100)
SVR24	39/41[b]	95% (88, 99)[b]	14/14	100%(85, 100)	NR	NR
On-treatment failure	0	0%	0	0%	0	0%
Relapse	0	0	0	0	0	0

BOC = boceprevir; CHC = chronic hepatitis C; DCV = daclatasvir; HCV = hepatitis C virus; n = number of patients; NR = not reported; PR = pegylated interferon plus ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment; TEL = telaprevir.

[a] Non-response defined as detectable HCV RNA levels at the end of treatment, viral breakthrough during treatment, or post-treatment relapse.

[b] Data were missing for two patients, both of whom had SVR at week 36 after the end of treatment.

Source: Sulkowski,[21] Clinical Study Report.[28]

TABLE 14: EFFICACY OUTCOMES FOR DACLATASVIR PLUS SOFOSBUVIR IN GENOTYPE 2 AND 3 CHRONIC HEPATITIS C (STUDY 040, ALLY-3)

Outcome/Subgroup	ALLY-3 Genotype 3 DCV + SOF 12 Weeks				Study 040 Genotype 2 or 3			
					DCV + SOF + RBV 24 Weeks		DCV + SOF 24 Weeks	
	Treatment-Naive		Treatment-Experienced		Treatment-Naive		Treatment-Naive	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (80% CI)	n/N	% (80% CI)
SVR12[a]	91/101	90% (83, 95)	44/51	86% (74, 94)	12/14[b]	86% (66, 96)	14/14[c]	100% (85, 100)[b]
SVR24[a]	NR		NR		13/14	93% (75, 99)	14/14	100% (85, 100)
SVR12 by fibrosis severity[d]					NR		NR	
No cirrhosis	73/75	97%	32/34	94%				
Cirrhosis	11/19	58%	9/13	69%				
Metavir F0 to F3	72/76	95%	39/43	91%				
Metavir F4	16/22	73%	5/8	63%				
SVR12 by prior treatment response[e]					NA		NA	
Relapse	NA		25/31	81%				
Partial response or viral breakthrough	NA		4/4	100%				
Null response	NA		7/7	100%				
Treatment-intolerant	NA		6/6	100%				
Other types of prior treatment failures	NA		2/3	67%				
On-treatment failure[f]	1/101	1%	0/51	0%	0	0%	0	0%
Relapse	9/100	9%	7/51	14%	0	0%	0	0%

CI = confidence interval; CHC = chronic hepatitis C; DCV = daclatasvir; HCV = hepatitis C virus; LLOQ = lower limit of quantification; N = number of patients; NA = not applicable; NR = not reported; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment.

[a] SVR12 or SVR24 defined as HCV RNA < LLOQ (detectable or undetectable) at 12 or 24 weeks, respectively, after the end of treatment.

[b] One patient had missing HCV RNA levels 12 weeks after the end of treatment, but had undetectable levels 24 weeks after treatment. One other patient was lost to follow-up.

[c] A total of 13 out of 14 patients (93%) achieved SVR12, defined as HCV RNA undetectable 12 weeks after the end of treatment.

[d] Cirrhosis status determined by liver biopsy at any time prior to screening, FibroScan (> 14.6 kPa) within 1 year of baseline, or FibroTest score ≥ 0.75 with aspartate aminotransferase to platelet ratio index > 2. Metavir score based on FibroTest assessment performed during screening (score > 0.74 = Metavir F4).

[e] Treatment-experienced patients received prior therapy with interferon alfa (with or without RBV), SOF + RBV, or other anti-HCV agents, such as inhibitors of cyclophilin or microRNA.

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

Source: Nelson,[22] Sulkowski,[21] Clinical Study Report.[28]

TABLE 15: EUROQOL 5-DIMENSIONS QUESTIONNAIRE DATA FOR DACLATASVIR PLUS SOFOSBUVIR IN GENOTYPE 3 CHRONIC HEPATITIS C PATIENTS (ALLY-3 STUDY)

Outcome/Subgroup	ALLY-3 Genotype 3 DCV + SOF 12 Weeks	
	Treatment-Naive	Treatment-Experienced
	Mean (SD), n	Mean (SD), n
EQ-5D index score		
Baseline	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]
Change from baseline to end of treatment	[redacted]	[redacted]
24 weeks post-treatment	[redacted]	[redacted]

CHC = chronic hepatitis C; DCV = daclatasvir; EQ-5D = EuroQol 5-Dimensions Questionnaire; SD = standard deviation; SOF = sofosbuvir.
Source: Clinical Study Report.[27]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To review the validity of sustained virologic response (SVR) at 12 weeks (SVR12) as a surrogate for SVR at 24 weeks (SVR24) and to summarize the characteristics of the EuroQol 5-Dimensions Questionnaire (EQ-5D) patient-reported outcome.

Findings

Sustained Virologic Response

SVR24 is the standard primary end point for assessing response to drugs that treat chronic hepatitis C (CHC) infection.[39] However, SVR12 is an emerging outcome of interest, potentially providing a means for determining treatment response earlier in either randomized controlled trials or the clinic. In 2013, the FDA published a paper that sought to determine the predictive value of SVR12 as a surrogate for SVR24.[39] The authors reviewed data submitted to the FDA (2002–2011) from 15 phase 2 and 3 studies that included various treatment durations of pegylated interferon alpha-2a, pegylated interferon alpha-2b, albinterferon alpha-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 SVR at 4 weeks (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.[39] 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.[39] They also stated these conclusions should be applied with caution to regimens that included only DAA drugs, considering they were based on data from regimens containing interferon plus ribavirin.[39] Further monitoring of interferon-free clinical trials may be required to determine the appropriate end point.

A study published in 2010 also evaluated the relevance of SVR12 as a primary outcome.[40] This study included 781 patients with CHC; all had received pegylated interferon plus ribavirin. Of the 781 patients, 573 had an end-of-treatment response and were thus included in the analysis. Of the 409 patients who had an SVR12, 408 went on to have an SVR24.[40] 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 pegylated interferon plus ribavirin.[41] The authors pooled single-group data for pegylated interferon alpha 2a or alpha 2b plus ribavirin from 35 clinical trials. Of these trials, only one study reported both SVR12 and SVR24. The proportion with an SVR12 or SVR24 was pooled across trials using a DerSimonian-Laird random-effects model. Data for SVR12, SVR24, and for each type of pegylated

interferon were pooled separately. The authors also performed a Bayesian random-effects meta-regression of the proportion with SVR12 or SVR24, controlling for the type of pegylated interferon. The authors concluded that SVR12 was 5% to 6% higher than SVR24, although the credible intervals 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).[41] These findings should be interpreted with caution considering they were based on data from a single treatment group. Naive pooling of single-group data is not an acceptable method to determine comparative efficacy, as it ignores the benefits of randomization and may therefore be subject to the same biases as a comparison of independent cohort studies. In addition, the analysis was limited to data from patients who received pegylated interferon plus ribavirin, 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, POITRON, FUSION, and VALENCE).[42] From this analysis, a total of 777 of 779 patients (99.7%) who achieved SVR12 also achieved SVR24, including all patients (n = 296) with HCC genotype 1 or 4 to 6, all patients (n = 270) with genotype 2, and 211 of 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%.

EuroQol 5-Dimensions Questionnaire

The EuroQol 5-Dimensions Questionnaire (EQ-5D) is a generic health-related quality-of-life (HRQoL) instrument that may be applied to a wide range of health conditions and treatments.[43,44] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[43,44] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system.
3. A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported minimum clinically important differences (MCIDs) for this scale have ranged from 0.033 to 0.074.[45] The MCID for the EQ-5D among CHC patients remains unknown.

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 sustained virologic response for regulatory approval.
- The generic EQ-5D HRQoL instrument has been widely used, but has not been properly validated in CHC. The MCID for the EQ-5D among CHC patients remains unknown.

APPENDIX 6: 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 matching-adjusted indirect comparisons (MAIC) for treatment-naive patients with hepatitis C virus (HCV) genotype 1 and genotype 3 submitted by the manufacturer.[20]

Summary of the Indirect Treatment Comparisons

Due to the lack of randomized controlled trials directly comparing the daclatasvir (DCV) + sofosbuvir (SOF) regimen versus other regimens of interest in patients chronically infected with HCV, indirect comparisons were performed in treatment-naive patients with HCV genotype 1 and patients with genotype 3. The outcomes assessed were sustained virologic response (SVR), discontinuation due to adverse events (AEs), and events of special interest, such as anemia and rash.

The manufacturer submitted MAIC to compare outcomes between trials while adjusting for baseline differences in trial populations. A Bayesian network meta-analysis (NMA) can be conducted when trials of different treatments can be linked together via randomized comparisons with the same reference treatment. The 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 groups are limited. When common reference groups are not available, anchor-based indirect comparisons, including NMAs, cannot be conducted. In these situations, the manufacturer used the MAIC to compare outcomes between trials while adjusting for baseline differences in trial populations. The MAIC method was used to adjust for cross-trial differences in baseline characteristics.

Treatment-Naive Patients With Hepatitis C Virus Genotype 1

One indirect treatment comparison (ITC) using the MAIC method estimated the comparative efficacy and safety of DCV + SOF ± ribavirin (RBV) with boceprevir (BOC), telaprevir (TEL), simeprevir (SIM) or SOF in combination with pegylated interferon plus ribavirin (PR).

Patients With Hepatitis C Virus Genotype 3

Three ITCs using the MAIC method estimated the comparative efficacy and safety of DCV + SOF with SOF + RBV and PR.

In addition, the manufacturer conducted one ITC using the MAIC method to estimate the comparative efficacy and safety of DCV + SOF ± RBV versus PR.

Methods

Eligibility Criteria

Treatment-Naive Patients With Hepatitis C Virus Genotype 1

Inclusion criteria for the review consisted of the following: phase 3 clinical trials in adult treatment-naive genotype 1 CHC patients treated with either SIM, SOF, BOC, or TEL plus PR. Included trials were required to report SVR results from clinical trials conducted in adult treatment-naive patients with chronic

genotype 1 HCV. The outcomes of interest were SVR and AEs. FDA-approved regimens of SIM, SOF, BOC, or TEL plus PR in treatment-naive genotype 1 patients were selected for the core analysis.

Patients With Hepatitis C Virus Genotype 3

For the comparison of DCV + SOF versus SOF + RBV and DCV + SOF versus PR, the inclusion criteria for the review consisted of the following: phase 3 or 4 clinical trials in adult treatment-naive and treatment-experienced genotype 3 CHC patients, treated with FDA and European Medicines Agency–approved SOF + RBV or PR regimens.

For the comparison of DCV + SOF ± RBV versus PR, interventional studies with adult treatment-naive patients infected with genotype 3 CHC patients were treated with the approved FDA treatment regimen for PR.

Indirect Treatment Comparisons

Treatment-Naive Patients With Hepatitis C Virus Genotype 1

The MAIC method to incorporate data from single-group studies into the ITC was used. Individual patient-level data were obtained from trials of DCV + SOF ± RBV from trial groups with treatment-naive genotype 1 patients. A propensity model was estimated to describe each patient's odds of enrollment 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, gender, race, genotype subtype, interleukin-28B gene (*IL28B*), plasma HCV ribonucleic acid (RNA) level, alanine transaminase (ALT) level, and presence or absence of cirrhosis. In the event 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 if the exclusion criteria were narrower than those of the comparator trial(s). Studies with dosing not consistent with the FDA label were excluded from the MAIC analysis. Treatment groups with the same regimens from different trials were pooled together.

Patients With Hepatitis C Virus Genotype 3

Individual patient-level data were obtained for trials for DCV + SOF and DCV + SOF ± RBV (from trial groups with treatment-naive genotype 3 patients). The same MAIC methods (described earlier) that were used to compare treatments in patients with HCV treatment–naive genotype 1 were also used in the comparison for this patient population.

For all analyses, individual patient-level data were drawn from the Bristol-Myers Squibb (BMS)-sponsored trials while systematic literature reviews to identify trials of the comparators regimens were conducted; however, 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).

Included Studies

Treatment-Naive Patients With Hepatitis C Virus Genotype 1

Individual patient-level data were obtained from the BMS trials of DCV + SOF ± RBV from trial groups with treatment-naive genotype 1 patients. 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

genotype 1 patients. The literature search seems to have missed one phase 3 study (OPTIMIZE) that used the TEL + PR regimen.

A total of seven trials were included in the MAIC analyses: DCV + SOF ± RBV (one trial); TEL + PR (two trials, n = 903); SIM + PR (two trials, n = 521); BOC + PR (one trial, n = 368); and SOF + PR (one trial, n = 327).

Enrollment criteria were the same between AI444-040 and the TEL, BOC, SOF, and SIM trials with two exceptions:

1. The AI444-040 study enrolled patients with an HCV RNA level of 100,000 IU/mL or higher at baseline, whereas the TEL trials enrolled patients with an HCV RNA greater than the limit of detection, and the SOF and BOC trials enrolled patients with an HCV RNA level greater than 10,000 IU/mL. The SIM trials did not report any inclusion criteria on baseline HCV RNA level.
2. The AI444-040 study excluded patients with evidence of cirrhosis at study entry (as documented by either a liver biopsy within the previous 24 months or a non-invasive assessment of serum markers of fibrosis), whereas SPRINT-2 excluded cirrhosis patients based on the results of biopsies performed within three years of screening, and the TEL, SOF, SIM trials all enrolled cirrhotic patients. However, 13.5% of treatment-naive genotype 1 patients enrolled in AI444-040 and 4.3% of patients treated with BOC for 24 weeks in SPRINT-2 had advanced fibrosis based on FibroTest scores at baseline.

Patients With Hepatitis C Virus Genotype 3

DCV + SOF

Individual patient-level data were obtained from the BMS trials of DCV + SOF from trial groups with genotype 3 patients. Systematic literature reviews were conducted to identify phase 3 or 4 clinical trials of the SOF + RBV or PR regimens in patients with genotype 3. The literature search seems to have identified all studies that meet the inclusion/exclusion criteria.

A total of four trials were included in the MAIC analysis of DCV + SOF versus SOF + RBV and DCV + SOF versus PR:

- DCV + SOF (one trial): ALLY-3 (n = 144 in comparison with SOF + RBV, and n = 74 in comparison with PR)
- SOF + RBV (one trial): n = 250
- PR (two trials): n = 492. Both trials included only treatment-naive patients.

Enrolment criteria were similar between ALLY-3 and the SOF + RBV trial and PR trials.

DCV + SOF ± RBV

Individual patient-level data were obtained from the BMS trials of DCV + SOF ± RBV from trial groups containing genotype 3 patients. Systematic literature reviews were conducted to identify clinical trials of PR regimens in patients with genotype 3.

A total of four trials were included in the MAIC analysis of DCV + SOF ± RBV versus PR: DCV + SOF (1 trial: AI444-040, n = 18), and PR (three trials, total n = 501 for efficacy; and one trial, n = 9 for safety).

Enrolment criteria were similar between AI444-040 and the PR trials with four exceptions:

1. Baseline HCV RNA: AI444-040 enrolled patients with an HCV RNA level of 100,000 IU/mL or higher at baseline, whereas two PR trials enrolled patients with an HCV RNA level greater than 600 IU/mL at baseline, and the third trial enrolled patients with an HCV RNA greater than the limit of detection.

2. ALT levels: two PR trials required patients to have elevated serum ALT levels; AI444-040 and the third PR trial did not have any ALT-level requirement.
3. Cirrhosis: The trials varied slightly on their exclusions for cirrhosis and other liver diseases.
4. Liver biopsy: one of the PR trials required patients to have liver biopsy findings consistent with chronic HCV infection; the other studies did not require a liver biopsy to validate chronic HCV infection.

Results

Treatment-Naive Patients With Hepatitis C Virus Genotype 1

The results of the MAIC procedure are presented in Table 16; these analyses are disjoint analyses of two treatments at a time. Estimates were interpreted as statistically significantly different if the 95% confidence interval of the risk difference did not include the null value of 0.

At 24 weeks post-treatment, patients treated with DCV + SOF ± RBV achieved statistically significantly higher SVR24 than patients treated with TEL + PR or BOC + PR, with and without applying MAIC. At 12 weeks post-treatment, patients treated with DCV + SOF ± RBV achieved statistically significantly higher SVR12 rates than patients treated with SOF + PR or SIM + PR, with and without applying MAIC.

After applying the MAIC method, patients treated with DCV + SOF ± RBV had statistically significantly lower rates of discontinuation due to AEs, anemia, and rash than patients treated with TEL + PR or SIM + PR. After applying the MAIC method, patients treated with DCV + SOF ± RBV had statistically significantly lower rates of discontinuation due to AEs and anemia, than those treated with BOC + PR. When compared with patients treated with SOF + PR, those treated with DCV + SOF ± RBV had statistically significantly lower rates of anemia. Discontinuation due to AEs did not significantly differ between these two groups. Comparison between DCV + SOF ± RBV and SOF + PR, or BOC + PR for rash was not reported.

In the sensitivity analyses that were conducted within the subpopulation of patients treated with DCV + SOF for 12 weeks without RBV, only 41 treatment-naive HCV genotype 1 patients (group G in study AI444-040) were included in this analysis. Results from this sensitivity analysis were similar to the core analysis in terms of efficacy and tolerability.

In the analysis where relevant phase 2 trials were included in the comparison, three additional phase 2 studies were included: one for TEL + PR, one for BOC + PR, and one for SIM + PR. No additional studies were identified for SOF + PR, hence, no comparison was conducted with SOF + PR in this analysis. Results from the comparison between DCV + SOF ± RBV and TEL + PR or BOC + PR were similar to the core analysis in terms of efficacy and tolerability. Also, results from the comparison between DCV + SOF ± RBV and SIM + PR were similar to the core analysis in terms of efficacy and tolerability except that discontinuation due to AE was not statistically significantly lower in the DCV + SOF ± RBV treatment group compared with the SIM + PR group. Also, results for the rash analysis were not reported for this comparison. In the sensitivity analyses that were conducted within the subpopulation of patients treated with SOF + DCV for 12 weeks without RBV, results from this sensitivity analysis were similar to the core analysis in terms of efficacy and tolerability; the only exception was that no results were reported for the rash analysis in the SOF + DCV for 12 weeks versus the SIM + PR comparison.

TABLE 16: MATCHING-ADJUSTED INDIRECT COMPARISON RESULTS FOR DCV + SOF ± RBV IN TREATMENT-NAIVE PATIENTS WITH GENOTYPE 1 CHRONIC HEPATITIS C

Outcome/Comparator		Percentage of Patients With Outcome[a]		Difference (%) DCV + SOF ± RBV Versus Comparator	
		Comparator	Adjusted DCV + SOF ± RBV	Adjusted Mean Difference	95% CI
SVR					
TEL + PR[b]		73.0	[redacted]	NR	[redacted]
BOC + PR[b]		66.6	[redacted]	NR	[redacted]
SIM + PR[c]		80.6	[redacted]	NR	[redacted]
SOF + PR[c]		89.6	[redacted]	NR	[redacted]
Adverse Events					
Discontinuation due to AE	TEL + PR	14.5	0.5	–14	(–17, –12)
	BOC + PR	12.2	0.1	–12	(–15, –9)
	SIM + PR	2.3	0.5	–2	(–3, 0)
	SOF + PR	1.5	0.8	–1	(–3, 1)
Anemia	TEL + PR	38.4	2.6	–36	(–40, –32)
	BOC + PR	49.5	1.9	–48	(–53, –42)
	SIM + PR	14.8	3.7	–11	(–15, –7)
	SOF + PR	20.8	7.2	–14	(–21, –6)
Rash	TEL + PR	37.1	15.4	–22	(–34, –9)
	BOC + PR	NR	NR	NR	NR
	SIM + PR	25.3	6.5	–19	(–25, –13)
	SOF + PR	NR	NR	NR	NR

AE = adverse event; BOC = boceprevir; CI = confidence interval; DCV = daclatasvir; NR = not reported; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; SVR = 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] Sustained virologic response 24 weeks after the end of treatment.

[c] Sustained virologic response 12 weeks after the end of treatment.

Patients With Hepatitis C Virus Genotype 3

The results of the MAIC procedure are presented in Table 17; these analyses are disjoint analyses of two treatments at a time. Estimates were interpreted as statistically significantly different if the 95% confidence interval of the risk difference did not include the null value of 0, or if the *P* value was less than 0.05.

A similar proportion of all patients treated with DCV + SOF and SOF + RBV achieved SVR12 with and without applying MAIC. Comparable results were observed in treatment-naive patients and previous non-responders. In the comparison using the ALLY-3 study, a significantly higher proportion of patients treated with DCV + SOF achieved SVR24 compared with patients treated with PR, both before and after applying MAIC.

Patients treated with DCV + SOF had statistically significantly lower rates of AEs and serious AEs than patients treated with SOF + RBV; however, there were no significant differences in the rates of discontinuation due to AEs. No patients in ALLY-3 discontinued due to AEs, in contrast with 4.3% of

genotype 2 and 3 patients in the pooled PR trials. While not significant before applying MAIC, this difference was statistically significant after applying MAIC ($P < 0.001$).

TABLE 17: MATCHING-ADJUSTED INDIRECT COMPARISON RESULTS FOR DCV + SOF IN PATIENTS WITH GENOTYPE 3 CHRONIC HEPATITIS C

Outcome/Comparator		Percentage of Patients With Outcome[a]		Difference (%) DCV + SOF Versus Comparator		
		Comparator	Adjusted DCV + SOF	Adjusted Mean Difference	95% CI	*P* Value
SVR						
SOF + RBV[b]		85.2	[redacted]	NR	[redacted]	[redacted]
SOF + RBV in treatment-naive patients[b]		94.3	[redacted]	NR	[redacted]	[redacted]
SOF + RBV in treatment-experienced patients[b]		78.6	[redacted]	NR	[redacted]	[redacted]
PR in treatment-naive patients[c]		66.5	[redacted]	NR	[redacted]	[redacted]
Adverse Events						
Discontinuation due to AE	SOF + RBV	0.4	[redacted]	[redacted]	NR	[redacted]
	PR	4.3	[redacted]	[redacted]	NR	[redacted]
Any AE	SOF + RBV	91.6	[redacted]	[redacted]	NR	[redacted]
Any serious AE	SOF + RBV	4	[redacted]	[redacted]	NR	[redacted]

AE = adverse event; DCV = daclatasvir; NR = not reported; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response 12 or 24 weeks after the end of treatment.
[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] Sustained virologic response 12 after the end of treatment.
[c] Sustained virologic response 24 after the end of treatment.

The results of the MAIC procedure are presented in Table 18. In the comparison using the AI444-040 study, a statistically significantly higher proportion of patients treated with DCV + SOF ± RBV achieved SVR24 than patients treated with PR, both with and without applying MAIC.

In the comparison of AEs between DCV + SOF ± RBV and PR, only 18 patients were included in the DCV + SOF ± RBV group and nine patients were included in the PR group. There was no significant difference in discontinuation due to AE and rash. There was significantly more influenza-like illness in the PR group than in the DCV + SOF ± RBV group.

TABLE 18: MATCHING-ADJUSTED INDIRECT COMPARISON RESULTS FOR DCV + SOF ± RBV IN TREATMENT-NAIVE PATIENTS WITH GENOTYPE 3 CHRONIC HEPATITIS C

Outcome/Comparator		Percentage of Patients With Outcome[a]		Difference (%) DCV + SOF ± RBV Versus Comparator		
		Comparator	Adjusted DCV + SOF ± RBV	Adjusted Mean Difference	95% CI	*P* Value
SVR						
PR[b]		66.1	[redacted]	NR	[redacted]	[redacted]
AEs						
Discontinuation due to AE	PR	0	0	NR	NR	NS
Rash	PR	11.1	2.8	NR	NR	NS
Influenza-like illness	PR	38.9	0	NR	NR	< 0.05

AE = adverse event; DCV = daclatasvir; NR = not reported; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response 12 or 24 weeks after the end of treatment.
[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] Sustained virologic response 24 weeks after the end of treatment.

Critical Appraisal

Critical Appraisal of the Matching-Adjusted Indirect Comparison

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 between the treatment groups of manufacturer-sponsored trials are matched with those of the comparison group from selected published trials.

The MAIC methods were also well reported; 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 more steps taken to adjust for missing data the for MAIC were explained.

However, there are several weaknesses to this method. In the literature, the MAIC technique has been used by only one person (the person who "invented" it and who also led this submission) and has not been the subject of any empirical/methods research. Also, 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 of the aspects one could consider appraising critically 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-group data was undertaken using disjoint analyses of two treatments at a time. Therefore, randomization had not been preserved and could result in biased estimates of treatment effect.

Treatment groups 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. In the comparison of DCV + SOF ± RBV with PR in patients with genotype 3, only nine patients were included in the analysis of AEs in the PR group, and only 18 patients were included in the DCV + SOF ± RBV group, hence, results from this analysis are difficult to interpret because they are based on very small sample sizes.

In the analysis of DCV + SOF ± RBV in patients with genotype 1, different doses and durations of DCV + SOF ± RBV were combined together; thus the true effect of the recommended dose is unclear. In addition, the draft product monograph indicates that DCV + SOF can be used in patients with genotype 1 who failed prior treatment with PR; however, no comparisons were made on treatment-experienced versus other regimens.

No comparisons were made for DCV + SOF ± RBV versus other regimens for patients with genotype 2; hence, the efficacy of DCV + SOF in comparison with other regimens is not known for this genotype.

Finally, the manufacturer-submitted ITC excluded two interferon-free regimens: ledipasvir + SOF and ombitasvir/paritaprevir/ritonavir and dasabuvir ± RBV, both of which were recently approved by Health Canada and are indicated for treatment-naive and treatment-experienced patients with HCV genotype 1. Thus, it is not possible to know the efficacy of DCV + SOF ± RBV versus these interferon-free regimens.

Summary

The manufacturer submitted another five ITCs using the MAIC technique for ITCs. This method was used to incorporate individual patient-level data from single-group studies in order to adjust for differences in baseline patient characteristics across separate study populations. With this method, in treatment-naive patients with HCV genotype 1, DCV + SOF ± RBV was associated with higher rates of SVR compared with TEL + PR, BOC + PR, SOF + PR, and SIM + PR. In patients with HCV genotype 3, DCV + SOF was associated with similar SVR rates as SOF + RBV in treatment-naive and treatment-experienced patients, but significantly higher SVR rates in treatment -naive patients treated with PR.

An important limitation of these ITCs is the absence of comparisons against two recently approved IFN-free regimens: ledipasvir + SOF and ombitasvir/paritaprevir/ritonavir with dasabuvir ± RBV. In addition, as with any indirect comparison, cross-trial differences in confounding factors could impact outcomes and lead to bias. As previously noted, there remains a lack of certainty as to the validity of incorporating single-group data in Bayesian NMAs, as well as uncertainty as to what the optimal methodological approach might be. Finally, it is also worth noting that there remains uncertainty regarding the performance of MAIC techniques for conducting 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.

APPENDIX 7: SAMPLE SIZE CALCULATIONS FOR THE INCLUDED STUDIES

Study	Efficacy	Harms
ALLY-3	Sample size of 100 treatment-naive or 50 treatment-experienced patients would provide a 95% CI for the observed SVR12 rates of within 9.7% and 14.2%, respectively, when the observed SVR12 rates were ≥ 75%. In the treatment-naive cohort, a target sample size of 100 patients would provide a 95% CI lower bound of > 76% with an observed SVR12 rate of 85%. In the treatment-experienced cohort, a target sample size of 50 patients would provide a 95% CI lower bound of > 73% with an observed SVR12 rate of 86%.	NR
040	With sample sizes of 14, 20, and 40 patients, the two-sided 80% exact CIs for a SVR12 were, respectively: • 585 to 92% if the observed rate was 79% (11 of 14 patients with an event) • 595 to 87% if the observed rate was 75% (15 of 20 patients with an event) • 645 to 84% if the observed rate was 75% (30 of 40 patients with an event).	Sample size of 14, 20, and 40 patients had a probability of 0.771, 0.878, and 0.985, respectively, of observing at least one safety event occurring at an incidence of 10%.

CI = confidence interval; NR = not reported; SVR12 = sustained virologic response 12 weeks after the end of treatment.
Source: Sulkowski,[21] Nelson,[22] Clinical Study Report.[27,28]

REFERENCES

1. Myers RP, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Can J Gastroenterol Hepatol [Internet]. 2014 May [cited 2015 Apr 2];28(5):243-50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4049256
2. Hepatitis C in Canada: 2005-2010 surveillance report. Executive summary [Internet]. Ottawa: Public Health Agency of Canada; 2012. [cited 2015 Apr 21]. Available from: http://www.phac-aspc.gc.ca/sti-its-surv-epi/hepc/surv-eng.php
3. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008 Aug;48(2):418-31.
4. Remis RS. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007: final report [Internet]. Ottawa: Public Health Agency of Canada; 2009. [cited 2015 Apr 2]. Available from: http://www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf
5. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010 Feb;138(2):513-21.
6. Centers for Disease Control and Prevention [Internet]. Atlanta (GA): Centers for Disease Control and Prevention. Surveillance for viral hepatitis - United States, 2011; 2013 Aug 19 [cited 2015 Apr 21]. Available from: http://www.cdc.gov/hepatitis/Statistics/2011Surveillance/Commentary.htm
7. Centre for Communicable Diseases and Infection Control, Infectious Disease Prevention and Control Branch. Hepatitis C in Canada: 2005-2010 surveillance report [Internet]. Ottawa: Public Health Agency of Canada; 2011. [cited 2015 Apr 21]. Available from: http://publications.gc.ca/collections/collection_2012/aspc-phac/HP40-70-2012-eng.pdf
8. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol [Internet]. 2012 Jun [cited 2015 Apr 2];26(6):359-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378284
9. Kamal SM. Acute hepatitis C: a systematic review. Am J Gastroenterol. 2008 May;103(5):1283-97.
10. Maheshwari A, Thuluvath PJ. Management of acute hepatitis C. Clin Liver Dis. 2010 Feb;14(1):169-76.
11. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. Lancet. 2008 Jul 26;372(9635):321-32.
12. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74.
13. Daklinza™ (daclatasvir dihydrochloride): 30 and 60 mg tablets [product monograph]. Saint-Laurent (QC): Bristol-Myers Squibb Canada; 2015 Jul 16.
14. Incivek® (telaprevir) 375 mg tablets [product monograph]. Laval (QC): Vertex Pharmaceuticals (Canada) Inc; 2013 Dec 17.
15. Victrelis® (boceprevir): 200 mg capsule [product monograph]. Kirkland (QC): Merck Canada Inc.; 2015 Feb 11.
16. Harvoni™ (ledipasvir/sofosbuvir): 90 mg/400 mg tablets [product monograph]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2014 Oct 14.
17. Sovaldi® (sofosbuvir): 400 mg tablets [product monograph]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2014 Dec 4.

18. Galexos™ (simeprevir): 150 mg capsules [product monograph]. Toronto: Janssen Inc.; 2015 Jan 29.
19. HOLKIRA™ PAK ombitasvir/paritaprevir/ritonavir film-coated tablets (12.5/75/50 mg) and dasabuvir film-coated tablets (250 mg) [product monograph] [Internet]. St-Laurent (QC): AbbVie Corporation; 2014 Dec 22. [cited 2015 Jul 7]. Available from: http://www.abbvie.ca/content/dam/abbviecorp/ca/english/docs/HOLKIRA_PAK_PM_EN.pdf
20. CDR submission: Daklinza™ (daclatasvir) tablets, 30 and 60 mg. Company: Bristol-Myers Squibb Canada [**CONFIDENTIAL** manufacturer's submission]. Saint-Laurent (QC): Bristol-Myers Squibb Canada; 2015 Feb 12.
21. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014 Jan 16;370(3):211-21.
22. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase 3 study. Hepatology. 2015 Apr;61(4):1127-35.
23. Kumada H, Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, et al. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. Hepatology [Internet]. 2014 Jun [cited 2015 Mar 13];59(6):2083-91. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315868
24. Jensen D, Sherman KE, Hezode C, Pol S, Zeuzem S, Ledinghen V, et al. Daclatasvir and asunaprevir plus peginterferon alfa and ribavirin in HCV genotype 1 or 4 non-responders. J Hepatol. 2015 Jul;63(1):30-7.
25. Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet. 2014 Nov 1;384(9954):1597-605.
26. Clinical Study Report: AI447031. A phase 3, comparative study of asunaprevir and daclatasvir (DUAL) combination therapy versus telaprevir therapy in Japanese genotype 1b chronic hepatitis C IFN eligible-naive subjects with a single arm assessment of DUAL therapy in IFN-therapy relapsers [**CONFIDENTIAL** internal manufacturer's report]. Princeton (NJ): Bristol-Myers Squibb Company; 2014 Apr 9.
27. Clinical Study Report: AI444218. A phase 3 evaluation of daclatasvir and sofosbuvir in treatment naive and treatment experienced subjects with genotype 3 chronic hepatitis C infection [**CONFIDENTIAL** internal manufacturer's report]. Princeton (NJ): Bristol-Myers Squibb Company; 2014 Dec 17.
28. Clinical Study Report: AI444040. Parallel, open-label, randomized study to evaluate the safety, pharmacokinetics, and pharmacodynamics of sofosbuvir (psi-7977) in combination with daclatasvir (bms-790052) with or without ribavirin in treatment naive subjects chronically infected with hepatitis C virus genotypes 1, 2, or 3 [**CONFIDENTIAL** internal manufacturer's report]. Hopewell (NJ): Bristol-Myers Squibb Company; 2013 Sep 2.
29. Clinical Study Report: AI447028. A phase 3 study with asunaprevir and daclatasvir (DUAL) for null or partial responders to peginterferon alfa and ribavirin (P/R), intolerant or ineligible to P/R subjects and treatment-naive subjects with chronic hepatitis C genotype 1b infection [**CONFIDENTIAL** internal manufacturer's report]. Princeton (NJ): Bristol-Myers Squibb Company; 2014 Feb 10.

30. Clinical Study Report: AI447026. A phase 3 Japanese study of BMS-790052 plus BMS-650032 combination therapy in chronic hepatitis C genotype 1b infected subjects who are non-response to interferon plus ribavirin and interferon based therapy ineligible naive/intolerant [**CONFIDENTIAL** internal manufacturer's report]. Princeton (NJ): Bristol-Myers Squibb Company; 2013 Sep 14.

31. Clinical Study Report: AI447029. A phase 3, open-label study with asunaprevir and daclastasvir plus pegintergeron alfa-2a (Pegasys) and ribavirin (Copegus) (P/R) (QUAD) for subjects who are null or partial responders to peginterferon alfa 2a or 2b plus ribavirin with chronic hepatitis C genotypes 1 or 4 infection [**CONFIDENTIAL** internal manufacturer's report]. Princeton (NJ): Bristol-Myers Squibb Company; 2014 Mar 5.

32. CDR submission: Sunvepraä (asunaprevir), 100 mg capsule. Company: Bristol-Myers Squibb [**CONFIDENTIAL** manufacturer's submission]. Saint-Laurent (QC): Bristol-Myers Squibb Canada; 2015 Feb.

33. Common Drug Review. Ledipasvir/sofosbuvir (Harvoni - Gilead Sciences Canada, Inc.) indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2015. (Clinical review report (in press)). [cited 2015 Jun 29]. Available from: https://www.cadth.ca/ledipasvir-sofosbuvir-4

34. Common Drug Review. Ombitasvir/paritaprevir/ritonavir and dasabuvir (Holkira PAK - AbbVie Corporation) indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2015. (Clinical review report (in press)). [cited 2015 Jun 29]. Available from: https://www.cadth.ca/ombitasvirparitaprevirritonavir-and-dasabuvir-4

35. Wyes D, Ruane P, Sulkowski M, Dieterich D, Luetkemeyer A, Morgan T, et al. Daclatasvir in combination with sofosbuvir for HIV/HCV coinfection: ALLY-2 study [Internet]. Abstract presented at: CROI 2015. Conference on Retroviruses and Opportunistic Infections (CROI); 2015 Feb 26; Seattle (WA). [cited 2015 Mar 13]. Available from: http://www.croiconference.org/sessions/daclatasvir-combination-sofosbuvir-hivhcv-coinfection-ally-2-study

36. Levin J. Conference reports for NaTaP: daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or post-transplant recurrence: ALLY-1 phase 3 study [Internet]. New York: National AIDS Treatment Advocacy Project; 2015 Apr. [cited 2015 Jul 15]. Available from: http://www.natap.org/2015/EASL/EASL_56.htm

37. CADTH. Direct-acting antiviral agents for chronic hepatitis C genotype 1 [Internet]. Ottawa: CADTH; 2014 Oct. (CADTH therapeutic review, volume 2, issue 2b). [cited 2015 Apr 2]. Available from: http://www.cadth.ca/media/pdf/TR0007_HepC_ScienceReport_e.pdf

38. CADTH. Drugs for chronic hepatitis C infection — project protocol [Internet]. Ottawa: CADTH; 2015 Apr. (CADTH Therapeutic Review vol.3, no.1a). [cited 2015 Jul 7]. Available from: https://www.cadth.ca/sites/default/files/pdf/tr0008_drugsforchronichepc.pdf

39. Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013 Jun;144(7):1450-5.

40. Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclere L, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology [Internet]. 2010 Apr [cited 2015 Jul 7];51(4):1122-6. Available from: http://onlinelibrary.wiley.com/doi/10.1002/hep.23444/pdf

41. Thorlund K, Druyts E, Mills EJ. SVR12 is higher than SVR24 in treatment-naive hepatitis C genotype 1 patients treated with peginterferon plus ribavirin. Clin Epidemiol [Internet]. 2014 [cited 2015 Jul 7];6:49-58. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3897323

42. Yoshida EM, Sulkowski MS, Gane EJ, Herring RW, Jr., Ratziu V, Ding X, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology. 2015 Jan;61(1):41-5.

43. Brooks R. EuroQol: the current state of play. Health Policy. 1996 Jul;37(1):53-72.

44. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

45. Sinnott PL, Joyce VR, Barnett PG. Guidebook: preference measurement in economic analysis [Internet]. Menlo Park (CA): Health Economics Resource Center; 2007. [cited 2015 Jul 7]. Available from: http://www.herc.research.va.gov/files/BOOK_419.pdf