Common Drug Review
Clinical Review Report

March 2016

Drug	ombitasvir, paritaprevir, ritonavir (Technivie)
Indication	In combination with ribavirin for the treatment of adults with genotype 4 chronic hepatitis C virus infection without cirrhosis who are either treatment naive or previously treated with peginterferon and ribavirin.
Listing request	As per indication
Dosage form(s)	Ombitasvir/paritaprevir/ritonavir film-coated tablets (12.5/75/50 mg) for oral administration
NOC date	20 October 2015
Manufacturer	AbbVie Corporation

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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

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

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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
CHC	chronic hepatitis C
CI	confidence interval
DAA	direct-acting antiviral agent
EQ-5D	EuroQol 5-Dimensions Questionnaire
EQ-5D-5L	EuroQol 5-Dimensions 5-Level Questionnaire
EQ-VAS	EQ visual analogue scale
HCV	hepatitis C virus
HCV-PRO	Hepatitis C Virus Patient-Reported Outcomes instrument
IFN	interferon
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IL28B	interleukin 28B genotype (CC or non-CC subtype)
LLOQ	lower limit of quantification
MCID	minimal clinically important difference
OBV	ombitasvir
PEG-IFN	pegylated interferon
PR	pegylated interferon plus ribavirin
PTV	paritaprevir
RBV	ribavirin
RTV	ritonavir
SAE	serious adverse event
SOF	sofosbuvir
SVR	sustained virologic response

EXECUTIVE SUMMARY

Introduction

In 2013, an estimated 250,000 Canadians had chronic hepatitis C (CHC) virus infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[1] There are six major hepatitis C virus (HCV) genotypes, of which genotype 1 infections are the most common in Canada (approximately 65%).[1] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada.[1] Genotype 4 is less common in Canada and accounts for less than 1% of HCV cases.[1] Hepatitis C most commonly affects people older than 30 years, and disproportionately affects 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 people 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 genotype 4 CHC.

The objective of this systematic review is to evaluate the efficacy and safety of ombitasvir, paritaprevir, and ritonavir (OBV/PTV/RTV) with or without ribavirin (RBV) for the treatment of genotype 4 HCV infection who are non-cirrhotic.

Indication under review
In combination with ribavirin for the treatment of adults with genotype 4 chronic hepatitis C virus infection without cirrhosis who are either treatment naive or previously treated with peginterferon and ribavirin.
Listing criteria requested by sponsor
As per indication

Results and Interpretation

Included Studies

One open-label, single-arm, phase 2 trial (PEARL-I [N = 316, of which 135 patients were non-cirrhotic HCV genotype 4 infected]) met the inclusion criteria for this systematic review. The trial included treatment-naive and pegylated interferon (PEG-IFN) plus RBV (PR) treatment-experienced genotype 4 CHC patients who were non-cirrhotic. The trial evaluated 12-week treatment with OBV/PTV/RTV with or without weight-based RBV. OBV/PTV/RTV with weight-based RBV for 12 weeks is the Health Canada–approved treatment regimen for the treatment of adults with genotype 4 CHC virus infection without cirrhosis who are either treatment-naive or were previously treated with PR. Health Canada also indicated that OBV/PTV/RTV for 12 weeks (without RBV) may be considered in treatment-naive patients who cannot take or tolerate RBV. The trial included a subset of patients randomized to two treatment groups (i.e., treatment-naive genotype 4 CHC patients were randomized to OBV/PTV/RTV plus weight-based RBV [N = 42] or to OBV/PTV/RTV [N = 44]), which was not powered by sufficient sample size. Forty-nine patients were included in the treatment arm of patients previously-treated with PR. The original design of the PEARL-I trial included an arm for treatment-experienced genotype 4 CHC patients who were to be treated with OBV/PTV/RTV; however, after the review of available data at post-

treatment week 4 for treatment-naive genotype 4 CHC patients, the trial design was amended and enrolment did not open for this group.

The primary efficacy outcome measure was the proportion of patients achieving sustained virologic response at 12 weeks (SVR12). Other outcomes included relapse rate and health-related quality of life (HRQoL). Key limitations included the lack of an active treatment comparator arm consisting of an existing treatment regimen for CHC genotype 4 infection. Limited data were available due to the small sample size.

Efficacy

The proportion of patients achieving SVR12 was 90.9% (95% confidence interval [CI], 78.3% to 97.5%) of treatment-naive patients treated with OBV/PTV/RTV without RBV, 100% (95% CI, 91.6% to 100.0%) of treatment-naive patients treated with OBV/PTV/RTV + RBV, and 100% (95% CI, 92.7% to 100.0%) of treatment-experienced patients treated with OBV/PTV/RTV + RBV. The regimen OBV/PTV/RTV without RBV was associated with lower rates of successful treatment in 90.9% of treatment-naive patients. The unadjusted SVR12 rate in treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV without RBV was lower by 9.09% (95% CI, 0.60% to 17.59%) than the SVR12 rate in treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV + RBV. When the Mantel–Haenszel method was used (the planned analysis) to adjust the comparison for differences in the proportion of interleukin 28B genotype (IL28B) CC subtype patients (versus non-CC), the estimate of the difference increased slightly to 9.16% (95% CI, –1.29% to 19.61%); however, the width of the 95% CI increased to include 0, which represents no statistically significant difference in SVR12 rates between the groups. However, the lack of statistical significance does not mean that a difference does not exist, especially given that the trial was not designed to find a statistically significant difference.

Three treatment-naive patients who received OBV/PTV/RTV without RBV had virologic failure: One patient had virologic breakthrough at treatment week 8, and two patients relapsed before post-treatment week 12. All three patients had resistance-associated variants present at the time of failure that were not present at baseline. The predominant variants in NS3 and NS5A were D168V and L28S or L28V, respectively. At post-treatment week 24, no new relapses were observed for patients with data. There was no relapse or virologic failure reported in the treatment groups of OBV/PTV/RTV + RBV.

The included trial evaluated HRQoL using two instruments, namely the EuroQol 5-Dimensions Questionnaire (EQ-5D) and the Hepatitis C Virus Patient-Reported Outcomes HCV-PRO instrument, which is an HCV-specific HRQoL instrument. The mean changes from baseline in HCV-PRO scores were statistically significantly lower in the OBV/PTV/RTV + RBV group than in the OBV/PTV/RTV without RBV groups at the final on-treatment visit, with lower scores indicating a poorer state of health. The differences in mean changes from baseline between these two groups were not statistically significant anymore at 24 weeks post-treatment. For EQ-5D, there were no statistically significant differences between treatment arms OBV/PTV/RTV + RBV and OBV/PTV/RTV without RBV within the trial. It should be noted that while no clinically meaningful changes occurred during treatment, there was also no substantive deterioration in HRQoL scores during treatment.

Despite the absence of direct comparative trials of OBV/PTV/RTV (with or without RBV) with other treatments for CHC infection, no indirect comparisons were submitted by the manufacturer. CADTH undertook a therapeutic review that provided estimates of the comparative efficacy of different regimens in patients with CHC genotype 4 infection.[8] It was found that in treatment-naive patients without cirrhosis, the rate of SVR12 for the reference treatment (PR) for 48 weeks was 0.65 (95% credibility interval [CrI], 0.63 to 0.67) and that OBV/PTV/RTV + RBV significantly increased SVR compared with PR for 48 weeks. There was no significant improvement in SVR when OBV/PTV/RTV + RBV, sofosbuvir (SOF) + RBV for 24 weeks, or SOF + PR for 12 weeks were compared (SOF + RBV for 24 weeks is not a Health Canada–approved indication, while SOF + PR for 12 weeks is an approved indication for this patient population). In treatment-experienced patients, the rate of SVR12 for the reference treatment (PR) for 48 weeks was 0.61 (95% CrI, 0.50 to 0.73). There was no significant improvement in SVR when OBV/PTV/RTV + RBV and SOF + RBV for 24 weeks were compared (SOF + RBV for 24 weeks is not a Health Canada–approved indication for this patient population).

Harms

Adverse events were frequent across all treatment groups in the included trial, ranging from 77.3% to 87.8%, with the most frequently reported adverse events being asthenia, headache, diarrhea, fatigue, insomnia, irritability, myalgia, nasopharyngitis, nausea, and pruritus. OBV/PTV/RTV + RBV was associated with a higher rate of adverse events than the OBV/PTV/RTV without RBV treatment group (88% versus 77%). No adverse events led to drug discontinuation in any treatment group. In addition, there was no death in any of the treatment groups. The rates of serious adverse events ranged from 0% to 2.3% across treatment groups in the included study.

Resistance emerged in three (6.8%) treatment-naive patients who received OBV/PTV/RTV without RBV. All three patients had resistance-associated variants present at the time of failure that were not present at baseline. The predominant variants in NS3 and NS5A were D168V and L28S or L28V, respectively.

The PEARL-I trial was 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

One pivotal open-label trial (PEARL-I) was included in this review. High rates of SVR12 were observed in treatment-naive and PR treatment-experienced genotype 4 CHC patients who were non-cirrhotic when OBV/PTV/RTV + RBV was administered. These SVR12 rates were higher than the SVR12 rates usually observed with PR treatment; however, PEARL-I did not include any control or active comparator arm and any comparisons are limited to indirect comparisons included in the CADTH Therapeutic Review report. HRQoL measures showed clinically insignificant changes from baseline, and differences between treatment groups were inconsistent between the different HRQoL measures. Characteristic adverse events associated with pegylated interferon appeared to occur less frequently among patients treated with OBV/PTV/RTV + RBV. The data from the PEARL-I trial were limited, due to the small numbers of patients treated.

TABLE 1: SUMMARY OF RESULTS

Outcome	PEARL-I		
	Treatment-Naïve Patients		Treatment-Experienced Patients
	OBV/PTV/RTV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks
SVR12			
n/N	40/44	42/42	49/49
% (95% CI)	90.9% (78.3 to 97.5)[a]	100% (91.6 to 100.0)[a]	100% (92.7 to 100.0)[a]
Unadjusted difference[a] % (95% CI)	With vs. without RBV: –9.09% (–17.59 to –0.60)		
Stratum-adjusted difference[b] (95% CI)	With vs. without RBV: –9.16% (–19.61 to 1.29)		
Relapse			
n/N	2/42	0	0
%	4.8%	0%	0%
EQ-5D-5L Health Index Score, Mean (SD)[c]			
Baseline	0.87	0.88	0.88
Change from baseline at final on-treatment visit	0.02 (0.1)	0.01 (0.1)	–0.02 (0.1)
LS Mean Difference (SE)[d]	With vs. without RBV: 0.01 (0.022)		
EQ-5D-5L VAS Score, Mean (SD)[e]			
Baseline	77.26	78.31	74.68
Change from baseline at final on-treatment visit	3.49 (9.3)	5.36 (16.3)	3.34 (17.0)
LS Mean Difference (SE)[d]	With vs. without RBV: –2.10 (2.446)		
HCV-PRO Score, Mean (SD)[f]			
Baseline	79.98	81.52	72.76
Change from baseline at final on-treatment visit	7.53 (7.4)	1.48 (14.1)	7.07 (18.4)
LS Mean Difference (SE)[d]	With vs. without RBV: 5.46 (2.214)		
Any AE			
n/N	34/44	37/42	43/49
%	77.3%	88.1%	87.8
SAEs			
n/N	1/44	0/42	0/49
%	2.3%	0%	0%
WDAEs			
n/N	0/44	0/42	0/49
%	0%	0%	0%

AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimensions 5-Level Questionnaire; HCV = hepatitis C virus; HCV-PRO = Hepatitis C Patient-Reported Outcomes; IFN = interferon; IL28B = interleukin 28B genotype; LS = least squares; OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SAE = serious adverse event; SD = standard deviation; SE = standard error; SVR12 = sustained virologic response 12 weeks after the end of treatment; VAS = visual analogue scale; vs. = versus; WDAE = withdrawal due to adverse event.

[a] CI constructed using the Clopper-Pearson exact method.

[b] Difference in rates after adjusting for IL28 genotype (CC or non-CC) using stratum-adjusted Mantel–Haenszel proportions and continuity-corrected variances.

[c] The EQ-5D-5L index score ranges from 0 to 1 (higher score is desirable), reflecting the societal perspectives on a certain health state.

[d] LS mean, 95% CI, and *P* value from ANCOVA model with treatment group as a factor and baseline score as a covariate.

[e] The EQ-5D-5L VAS score ranges from 0 to 100, where 0 = worst imaginable health state and 100 = best imaginable health state.

[f] The HCV-PRO total score ranges from 0 to 100, with a higher score being desirable.

Source: Hezode et al.,[9] Clinical Study Report for PEARL-I.[10]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hepatitis C infection is caused by an enveloped, single-stranded linear ribonucleic acid (RNA) virus of the *Flaviviridae* family. In 2013, an estimated 250,000 Canadians had chronic hepatitis C virus (HCV) infection, but the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[1] A total of 11,357 cases of HCV, most due to injection drug use, were reported in Canada in 2009.[2] Hepatitis C most commonly affects people older than 30 years of age and disproportionately men, although the gender gap is narrowing.[2] Other populations at higher risk for HCV infection include federal inmates, men who have sex with men, street-involved youth, and Aboriginal peoples.[2] There are six major HCV genotypes, of which genotype 1 infections are the most common in Canada (approximately 65%).[1] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada.[1] Genotype 4 is less common in Canada and accounts for less than 1% of HCV cases.[1]

Of the people infected, approximately 25% clear infection spontaneously (range 15% to 45%) and the remainder develop chronic infection.[11-13] 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, human immunodeficiency virus (HIV) co-infection, obesity, and increasing age are associated with an increased risk of liver disease progression.[3,14] While the incidence of HCV infection appears to be stable or declining in North America and Canada, it is expected that liver-related morbidity and mortality will continue to increase over the coming decades, as those who are already infected age.[1,4-7]

1.2 Standards of Therapy

Until recently, pegylated interferon plus ribavirin (RBV) (PR) administered for 48 weeks was the gold-standard therapy for patients with CHC infection with genotype 4.[15] The Canadian Association for the Study of the Liver (CASL) updated its Consensus Guidelines in early 2015, citing the need to adjust its recommendations based on the rapidly changing treatment landscape and the dramatically improved rates of virologic clearance found in studies of the new direct-acting antiviral (DAA) agents.[15] The guidelines recommend the interferon-free DAA regimens (sofosbuvir plus ledipasvir [SOF/LDV], and ombitasvir plus paritaprevir plus ritonavir [OBV/PTV/RTV] plus ribavirin [RBV]) for the treatment of patients with CHC genotype 4 infection. SOF/LDV is not currently indicated for genotype 4 in Canada. The CASL Consensus Guidelines also suggest an alternative interferon-free regimen (SOF + RBV) and interferon-containing regimens (SOF + PR and simeprevir (SIM) + PR) be used for the treatment of patients with CHC genotype 4 infection. The CASL Consensus Guidelines do not recommend the use of PR alone for the treatment of patients with CHC genotype 4 infection.[15] The recommendation from the CADTH Canadian Drug Expert Committee (CDEC) on the CADTH Therapeutic Review report, *Drugs for Chronic Hepatitis C Infection*,[16] for patients with genotype 4 is SOF + PR for 12 weeks in treatment-naive non-cirrhotic patients. There was insufficient evidence to make a recommendation for other patients with genotype 4. OBV/PTV/RTV was not included in the recommendation because Technivie did not have a Notice of Compliance (NOC) at the time the recommendations were issued.[16]

1.3 Drug

Technivie is a combination of OBV, PTV, and RTV. These are the same components as an alternative treatment previously reviewed by CADTH Common Drug Review (CDR) for genotype 1 CHC, Holkira Pak, but without dasabuvir. Technivie consists of one combination tablet containing 12.5 mg OBV, 75 mg

PTV, and 50 mg RTV. The dosage is two tablets daily of the combination tablet. RBV is indicated with OBV/PTV/RTV in non-cirrhotic patients with genotype 4 infection. Treatment-naive patients who cannot take or tolerate RBV may consider Technivie without RBV for 12 weeks.[17]

Indication under review
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TABLE 2: KEY CHARACTERISTICS OF DIRECT-ACTING ANTIVIRAL AGENTS APPROVED FOR USE IN CANADA

	OBV/PTV/RTV	SOF	LDV	SIM
Mechanism of Action	OBV: HCV NS5A inhibitor that inhibits viral replication PTV: HCV NS3/4A protease inhibitor that inhibits viral replication RTV: pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of PTV. It is not active against HCV.	HCV NS5B polymerase inhibitor. The NS5B polymerase is an RNA polymerase that is critical for the viral replication cycle.	HCV NS5A inhibitor. The NS5A protein is an essential component of HCV replicase even though no known enzymatic function has been associated with it.	HCV NS3/4A protease inhibitor: The protease is essential for viral replication.
Indication[a]	Treatment of CHC genotype 4 infection in adults without cirrhosis	Treatment of genotype 4 CHC infection in combination with PR	In combination with SOF for the treatment of genotype 1 CHC infection in adults. Not recommended for genotype 4	Treatment of CHC genotype 4 infection, in combination with PR, in adults with compensated liver disease Also treatment of CHC genotype 4 infection, in combination with SOF, in treatment-naive, prior relapse patients, and prior non-responder adult patients, with or without cirrhosis, who are not co-infected with HIV
Route of Administration	Oral	Oral	Oral	Oral
Recommended Dose	Two OBV/PTV/RTV 12.5/75/50 mg tablets taken once daily for 12	400 mg tablet, once daily with PR for 12 weeks	SOF/LDV 400/90 mg once daily for 12 weeks	150 mg capsule once daily with PR

	OBV/PTV/RTV	SOF	LDV	SIM
	weeks. OBV/PTV/RTV administered without RBV for 12 weeks may be considered for treatment-naive patients who cannot take or tolerate RBV			**Treatment-Naive:** Triple therapy for 12 weeks, followed by PR for additional 12 weeks **Treatment-Experienced:** Triple therapy for 12 weeks, plus PR for additional 36 weeks **Cirrhotic patients:** As per above; no special dosing. 150 mg/400 mg SIM/SOF once daily for 12 weeks, with treatment for up to 24 weeks duration, should be considered in patients with cirrhosis.
Serious Side Effects or Safety Issues	Fatigue, headache, nausea, pruritus and insomnia	Fatigue, headache PR is associated with adverse events: anemia, sleep loss, depression, rash, headaches, nausea, severe fatigue.	Fatigue, headache	Rash, pruritus, nausea PR is associated with adverse events: anemia, sleep loss, depression, rash, headaches, nausea, severe fatigue.

CHC = chronic hepatitis C; HIV = human immunodeficiency virus; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RNA = ribonucleic acid; RTV = ritonavir; SIM = simeprevir; SOF = sofosbuvir.

[a] Health Canada indication.

Source: Product monographs.[17-20]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of OBV/PTV/RTV for the treatment of CHC genotype 4 infection in adults without cirrhosis who are either treatment-naive or previously treated with PR.

2.2 Methods

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

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with CHC genotype 4 infection who are without cirrhosis Subpopulations: • Treatment history (treatment-naive, or prior relapse, partial response, null response, intolerant to, or ineligible to receive PR or DAA agent therapy) • Fibrosis level • HIV co-infection • Hepatitis B co-infection • Renal insufficiency • Liver transplant
Intervention	Two OBV/PTV/RTV 12.5/75/50 mg once daily, with RBV[a]
Comparators	• sofosbuvir in combination with PR • simeprevir in combination with PR • simeprevir in combination with sofosbuvir • placebo in combination with PR • placebo/no treatment
Outcomes	**Key efficacy outcomes:** • Sustained virologic response • Virologic failure • 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, nausea)
Study Design	Published and unpublished phase 3 RCTs

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

[a] OBV/PTV/RTV administered without RBV for 12 weeks may be considered for treatment-naive patients who cannot take or tolerate RBV.

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

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

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

The initial search was completed on October 5, 2015. Regular alerts were established to update the search until the meeting of CDEC on February 15, 2016. Regular search updates were performed on databases that do not provide alert services.

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

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4 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

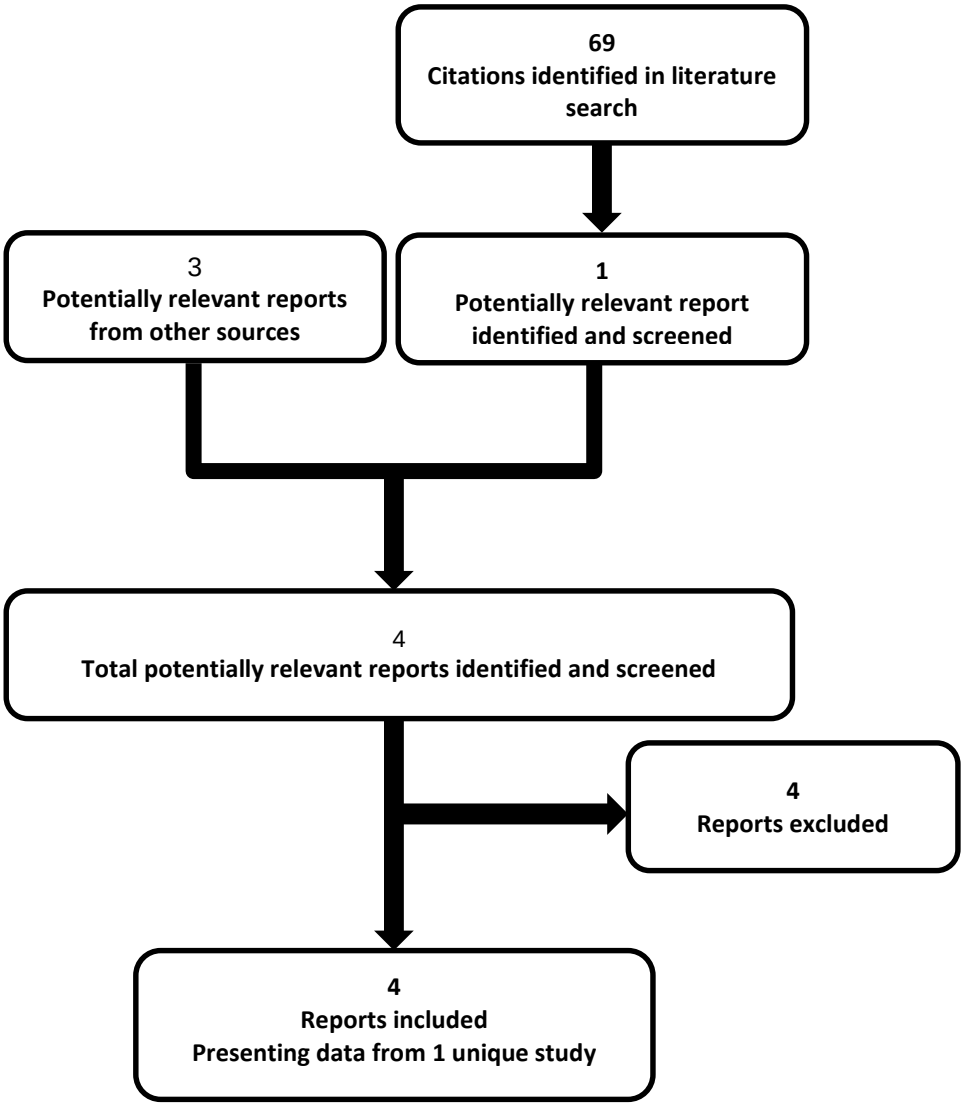


TABLE 4: DETAILS OF INCLUDED STUDY

		PEARL-I
DESIGNS AND POPULATIONS	**Study Design**	Open-label, single-arm, randomized (1 randomization for treatment-naive genotype 4 patients to RBV yes/no)
	Locations	Europe, Puerto Rico, US
	Enrolled (N)	A total of 316 patients were enrolled (135 patients were non-cirrhotic HCV genotype 4 infected).
	Inclusion Criteria	Adults with CHC who were 18 to 70 years of age and were either: • Treatment-naive or treatment-experienced[a] with genotype 1b with or without cirrhosis for at least 6 months before study screening • Treatment-naive or treatment-experienced[a] with genotype 4 infection without cirrhosis for at least 6 months before study screening. • Patients had to have plasma HCV RNA level > 10,000 IU/mL at screening.
	Exclusion Criteria	• Co-infection with HIV or hepatitis B • History of severe, life-threatening or other significant sensitivity to any drug • Females who were pregnant or planned to become pregnant, or who were breastfeeding, or genotype 4–infected males whose partners were pregnant or planning to become pregnant within 7 months after their last dose of study drug or RBV • Previous use of any investigational or commercially available anti-HCV agents other than PR therapy in treatment-experienced patients • Recent history of drug or alcohol abuse • Any cause of liver disease other than chronic HCV infection • History of solid organ transplant • Cirrhosis for patients with genotype 4 (liver biopsy within 24 months before screening or during screening demonstrating the absence of cirrhosis. In the absence of a biopsy within the 24 months before screening or during screening, then a screening FibroTest score of ≤ 0.72 and AST to platelet ratio index (APRI) ≤ 2, or a screening FibroScan result of < 9.6 kPa was used.) • CrCl < 60 mL/min • HCC
DRUGS	**Intervention**	*Treatment-naive G4* 12 weeks of treatment with the combination of 1 tablet 25 mg OBV, 3 tablets 50 mg PTV, and 1 capsule 100 mg RTV once daily plus RBV (weight-based dosing)[b] or 12 weeks of treatment with the combination of 1 tablet 25 mg OBV, 3 tablets 50 mg PTV, and 1 capsule 100 mg RTV once daily *Treatment-experienced G4* 12 weeks of treatment with the combination of 1 tablet 25 mg OBV, 3 tablets 50 mg PTV, and 1 capsule 100 mg RTV once daily plus RBV (weight-based dosing)[b] *Treatment-naive G1b* 12 weeks of treatment with the combination of 1 tablet 25 mg OBV, 3 tablets 50 mg PTV, and 1 capsule 100 mg RTV once daily *Treatment-experienced (null responder) G1b* 12 weeks of treatment with the combination of 1 tablet 25 mg OBV, 3 tablets 50 mg PTV, and 1 capsule 100 mg RTV once daily *Treatment-naive G1b with compensated cirrhosis* 24 weeks of treatment with the combination of 1 tablet 25 mg OBV, 3 tablets 50 mg PTV,

		PEARL-I
		and 1 capsule 100 mg RTV once daily *Treatment-experienced G1b with compensated cirrhosis* 24 weeks of treatment with the combination of 1 tablet 25 mg OBV, 3 tablets 50 mg PTV, and 1 capsule 100 mg RTV once daily
	Comparator(s)	None
DURATION	**Phase**	2
	Run-in	Up to 35 days
	Open-label	12 to 24 weeks
	Follow-up	48 weeks
OUTCOMES	**Primary End Point**	SVR12
	Other End Points	SVR24 Virologic failure Relapse HCV-PRO EQ-5D-5L Harms
NOTES	**Publications**	Hezode et al. 2015[9]

AST = aspartate aminotransferase; CHC = chronic hepatitis C; CrCl = creatinine clearance; EQ-5D-5L = EuroQol 5-Dimensions 5-Level Questionnaire; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HCV-PRO = HCV Patient-Reported Outcomes; HIV = human immunodeficiency virus; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment.

[a] Treatment-experienced defined as prior null responders, partial responders, or relapsers to PR.

[b] Either 1,000 mg or 1,200 mg daily divided twice daily per local label (e.g., < 75 kg = 1,000 mg daily divided twice daily or ≥ 75 kg = 1,200 mg daily divided twice daily).

Note: Two additional reports were included.[21,22]

Source: Hezode et al.,[9] Clinical Study Report for PEARL-I.[10]

3.2 Included Studies

3.2.1 Description of Studies

One pivotal phase 2 multi-centre open-label trial (PEARL-I) was included in this systematic review (Table 4). The PEARL-I trial evaluated OBV/PTV/RTV with or without weight-based RBV for 12 weeks among treatment-naive and PR treatment-experienced genotype 4 CHC patients. Enrolment did not open for the group of treatment-experienced genotype 4 CHC patients to be treated with OBV/PTV/RTV. This decision was made after the review of available data at post-treatment week 4 for treatment-naive genotype 4 CHC patients from PEARL-I study, in which none of 10 treatment-naive genotype 4 CHC patients completing treatment with OBV/PTV/RTV + RBV experienced virologic failures, but two of 10 treatment-naive genotype 4 CHC patients who received OBV/PTV/RTV without RBV experienced virologic failure (one breakthrough and one relapse). After this analysis, the decision was made to open enrolment to the PR treatment-experienced genotype 4 CHC patients, but only to the regimen with RBV. One randomization for treatment-naive genotype 4 CHC patients was made, where patients were randomized to OBV/PTV/RTV with or without weight-based RBV. The randomization schedule was stratified by interleukin 28B genotype (subtypes CC versus non-CC). The primary outcome was sustained virologic response 12 weeks after the last actual dose of study drug (SVR12). An SVR12 comparison was done between treatment-naive genotype 4 CHC patients who received OBV/PTV/RTV + RBV versus treatment-naive genotype 4 CHC patients who received OBV/PTV/RTV.

The product monograph indicates that OBV/PTV/RTV without RBV for 12 weeks may be considered for treatment-naive patients who cannot take or tolerate RBV. However, in the study design and inclusion and exclusion criteria, such patients were not identified; hence, patients who were included in the study arm of OBV/PTV/RTV without RBV for 12 weeks would be able to take and tolerate RBV.

The PEARL-I trial included additional cohorts that did not meet this review's inclusion criteria, and these groups have not been summarized in this report. In these groups, OBV/PTV/RTV for 12 weeks was evaluated among treatment-naive and prior PR null responder genotype 1b CHC patients without cirrhosis and OBV/PTV/RTV for 24 weeks among treatment-naive and PR treatment-experienced genotype 1b CHC patients with compensated cirrhosis. CDEC has previously recommended Holkira Pak for treatment-experienced genotype 1 CHC patients with compensated cirrhosis.[23]

3.2.2 Populations

a) Inclusion and exclusion criteria

The main inclusion and exclusion criteria for the included trial are summarized in Table 4.

The included trial recruited adult patients with chronic HCV infection. Chronic HCV infection was defined by either being positive for anti-HCV antibody or HCV RNA at least six months before screening and positive for HCV RNA and anti-HCV antibody at the time of screening or being positive for anti-HCV antibody and HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrolment with evidence of chronic HCV disease). Patients had to have plasma HCV RNA levels greater than 10,000 IU/mL at screening. Patients of child-bearing age had to use two effective methods of birth control while receiving study drugs and for seven months after stopping study drugs. Patients enrolled with HCV genotype 4 infection also met the following criteria: liver biopsy within 24 months before screening or during screening demonstrating the absence of cirrhosis; in the absence of a biopsy within the 24 months before screening or during screening, then a screening FibroTest score of ≤ 0.72 and aspartate aminotransferase to platelet ratio index ≤ 2 or a screening FibroScan result of < 9.6 kPa was used. Another inclusion criterion in the included trials was that patients had to have a body mass index of ≥ 18 to < 38 kg/m^2 at the time of screening.

Patients were excluded from trials if they had hepatitis B or HIV co-infection, other causes of liver disease, history of solid organ transplant, current or past clinical evidence of cirrhosis, uncontrolled seizures, uncontrolled diabetes, or a creatinine clearance < 60 mL/min.

The PEARL-I trial included a mix of patients who had prior experience with PR treatment and patients who were treatment-naive. Failure to prior experience with PR was defined by one of the following categories:

- ***Null responders:*** Patient had documentation that they previously received PR for at least 10 weeks and failed to achieve a 2 $\log_{10}$ IU/mL HCV RNA decrease at week 12;
- ***Partial responders:*** Patient received at least 20 weeks of PR for the treatment of HCV and achieved ≥ 2 $\log_{10}$ reduction in HCV RNA at week 12, but failed to achieve HCV RNA undetectable at the end of treatment; or
- ***Relapsers:*** Patient received at least 36 weeks of PR for the treatment of HCV and HCV RNA was undetectable at the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up.

b) Baseline characteristics

Baseline characteristics for the included trials are summarized in Table 5.

The majority of patients were male and Caucasian. The mean treatment age of treatment-naive patients was slightly lower than that of treatment-experienced patients. The vast majority of patients had a METAVIR score F0 to F1; the proportion of patients with METAVIR score F2 to F4 ranged from 13.6% in treatment-naive patients treated with OBV/PTV/RTV to 32.6% in treatment-experienced patients treated with OBV/PTV/RTV + RBV. PEARL-I included patients with previous exposure to PR; 46.9% of patients were null responders to this treatment, followed by the relapsers (34.7%), and partial responders were the least represented (18.4%). Due to small enrolment numbers, percentage differences observed in some baseline characteristics were dramatically affected by small differences in numbers of patients (i.e., race and METAVIR score).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	PEARL-I		
	Treatment-Naive Patients		Treatment-Experienced Patients
	OBV/PTV/RTV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks
N	44	42	49
Age, Mean (SD)	49 (10)	44 (13)	51 (10)
Male, n (%)	24 (54.5)	28 (66.7)	36 (73.5)
Race, n (%)			
Caucasian	37 (84.1)	38 (90.5)	45 (91.8)
Black	6 (13.6)	3 (7.1)	3 (6.1)
Other	1 (2.3)	1 (2.4)	1 (2.0)
Genotype, n (%)			
HCV 4	44 (100)	42 (100)	49 (100)
IL28B_CC	12 (27.3)	11 (26.2)	6 (12.2)
IL28B_CT	24 (54.5)	26 (61.9)	32 (65.3)
IL28B_TT	8 (18.2)	5 (11.9)	11 (22.4)
Baseline HCV RNA			
log_{10} IU/mL, mean (SD)	6.10 (0.58)	6.11 (0.59)	6.27 (0.49)
≥ 800 000 IU/mL	27 (61.4)	30 (71.4)	37 (75.5)
Prior Treatment Status			
Treatment-naive	44 (100)	42 (100)	NA
Treatment-experienced	NA	NA	49 (100)
Previous Response to PR Treatment			
Null responder	NA	NA	23 (46.9)
Partial responder	NA	NA	9 (18.4)
Relapser	NA	NA	17 (34.7)
METAVIR Score			
F0-F1	38 (86.4)	33 (78.6)	33 (67.3)
F2	4 (9.1)	6 (14.3)	11 (22.4)
F3	2 (4.5)	2 (4.8)	5 (10.2)

	PEARL-I		
	Treatment-Naive Patients		Treatment-Experienced Patients
	OBV/PTV/RTV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks
F4	0	1 (2.4)	0

HCV = hepatitis C virus; IL28B = interleukin 28B genotype, subtype CC, CT or TT; IU = international unit; NA = not applicable; OBV = ombitasvir; PR = pegylated interferon plus ribavirin; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SD = standard deviation.
Source: Hezode et al.,[9] Clinical Study Report for PEARL-I.[10]

3.2.3 Interventions

All trial arms evaluated the same test intervention, which consisted of 12 weeks of treatment with the combination of one tablet of 25 mg OBV, three tablets of 50 mg PTV, and one capsule of 100 mg RTV once daily with or without RBV. RBV was dosed by weight, with patients < 75 kg receiving 1,000 mg daily, and patients ≥ 75 kg receiving 1,200 mg daily, both divided into two oral doses.

3.2.4 Outcomes

The primary outcome was SVR12. Other outcomes reported were the proportion of patients with SVR24, relapse, virologic failure during treatment, quality of life, and adverse events.

HCV RNA levels were collected weekly for the first four weeks, then every two weeks during treatment, at the end of treatment, and at post-treatment weeks 2, 4, 8, 12, 24, and 48.

SVR12 was defined as HCV RNA levels less than the lower limit of quantification (LLOQ) 12 weeks after the last actual dose of study drug.

SVR24 was defined as HCV RNA levels less than LLOQ 24 weeks after the last actual dose of study drug.

Post-treatment relapse (defined as confirmed HCV RNA greater than or equal to LLOQ between end of treatment and 12 weeks after the last dose of study drugs among patients who completed treatment with HCV RNA less than LLOQ at the end of treatment).

Virologic failure during treatment (defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, confirmed increase from nadir in HCV RNA [two consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir] during treatment, or all measurements of HCV RNA ≥ LLOQ during treatment, with at least six weeks [≥ 36 days] of treatment).

Health-related quality of life (HRQoL) evaluation was performed frequently throughout the trial and in post-treatment follow-up. HRQoL was measured using the EuroQol 5-Dimensions 5-Level Questionnaire (EQ-5D-5L) and the Hepatitis C Virus Patient-Reported Outcomes (HCV-PRO) instrument. HRQoL was evaluated at each visit. APPENDIX 5 summarizes the validity of these three measures in HCV patients. The minimal clinically important difference (MCID) for the EQ-5D-5L among CHC patients remains unknown. An MCID of –10 points was reported for HCV-PRO.

3.2.5 Harms

An adverse event was defined as any untoward medical occurrence in a study patient administered a pharmaceutical product and that did not necessarily have a causal relationship with the treatment. An adverse event could therefore have been any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event was considered causally related to the use of the product.

3.2.6 Statistical Analysis

While a sample size calculation was completed for the genotype 1b portion of the study, no sample size calculation was undertaken for patients with genotype 4 CHC infection.

Treatment-naive patients with genotype 4 CHC were randomized in a 1:1 ratio to OBV/PTV/RTV for 12 weeks and OBV/PTV/RTV + RBV for 12 weeks. The randomization schedule was stratified by interleukin 28B (IL28B) genotype (CC versus non-CC subtypes). An interim analysis of all data was completed after all non-cirrhotic patients reached post-treatment week 12 or prematurely discontinued from the study. No statistical adjustment was employed due to these analyses as this was an open-label trial and no changes in trial design were planned or performed as a result of the interim analyses.

A pairwise comparison between the 12-week OBV/PTV/RTV + RBV regimen and the 12-week OBV/PTV/RTV regimen without RBV among the CHC genotype 4 infected treatment-naive patients was undertaken.

Treatment differences (with 95% confidence intervals [CIs]) for the comparisons between the 12-week OBV/PTV/RTV regimen with and without RBV among CHC genotype 4 infected treatment-naive patients were estimated using stratum-adjusted Mantel–Haenszel proportion and continuity-corrected variance, adjusting for IL28B genotype (subtypes CC or non-CC).

For each treatment group, the number and percentage of patients with SVR12 were summarized along with exact 95% CIs.

The change from baseline to final treatment visit and post-treatment week 24 in the HCV-PRO total score, the EQ-5D-5L health index score, and the EQ-5D-5L visual analogue score (EQ-VAS) were performed using an analysis of covariance (ANCOVA) with factors for treatment group and baseline score.

No data were imputed for any efficacy or safety analysis except for the patient-reported outcomes questionnaires and for all analyses of SVR and rapid virologic response. For HCV-PRO, if a respondent answered at least 12 of the 16 items, the missing items were imputed with the average score of the answered items. In cases where the respondent did not answer five or more items, the total score was considered missing. For EQ-5D-5L, no imputation was performed for missing items.

HCV RNA values were selected for analysis based on the defined visit windows. When there was no HCV RNA value in a defined visit window, the closest values before and after the window were used for flanking imputation, regardless of the value chosen for the subsequent and preceding windows. For flanking imputation, if a patient had a missing HCV RNA value at a post-baseline visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and the succeeding value, the HCV RNA level was considered undetectable or unquantifiable, respectively, at this visit for this patient. Subsequent to this flanking imputation, if a patient was missing a value for the visit window associated with the analysis, the patient was imputed as a failure. Following the flanking imputation for SVR analyses (e.g., SVR12, SVR24), if there was no value in the appropriate window after the flanking imputation but there was an HCV RNA value after the window, then it was imputed into the SVR window. If a patient was still missing a value for the window associated with the SVR analysis after the imputation, the patient was imputed as a failure.

Subgroup analyses by METAVIR scores (F0–F1, F2, F3, and F4) and prior HCV treatment history were performed. The CDR review protocol included subgroups by ineligibility to receive PR or DAA therapy, HIV co-infection, hepatitis B co-infection, renal insufficiency, and liver transplant; however, such subgroup analyses were not undertaken because patients who would fall into each of these subgroups except for the ineligibility to receive PR were excluded from the trial.

a) Analysis populations

The intention-to-treat and safety analysis sets included all patients who received at least one dose of study drug. Efficacy analyses were performed on the intention-to-treat population, whereas safety, demographics, baseline characteristics, and exposure analyses were performed on the safety population according to actual treatment received even if different from the treatment assignment. Because all patients received the treatment to which they were assigned, the safety population is the same as the intention-to-treat population.

3.3 Patient Disposition

Table 6 summarizes patient disposition in the included trial.

None of the patients who received OBV/PTV/RTV + RBV discontinued the study drug; two (4.5%) patients who received OBV/PTV/RTV without RBV discontinued treatment, with one patient discontinuing treatment due to virologic failure and the second patient discontinuing due to loss of follow-up. Three patients (6.8%) in the OBV/PTV/RTV without RBV study arm and one patient in the treatment-naive OBV/PTV/RTV + RBV study arm discontinued the study due to loss of follow-up. No patient in the treatment-experienced group who received OBV/PTV/RTV + RBV discontinued the study.

TABLE 6: PATIENT DISPOSITION

	PEARL-I		
	Treatment-Naive Patients		Treatment-Experienced Patients
	OBV/PTV/RTV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks
Screened, N	174		
Randomized, N (%)	44	42	49
Treated, N (%)	44	42	49
Discontinued Study Drug, N (%)	2 (4.5)	0	0
Lost to follow-up	1 (2.3)	0	0
Virologic failure	1 (2.3)[a]	0	0
Discontinued Study, N (%)	3 (6.8)	1 (2.4)	0
Lost to follow-up	3 (6.8)[b]	1 (2.4)[b]	0
ITT, N	44	42	49
Safety, N	44	42	49

ITT = intention-to-treat; OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir.
[a] Continued the study in the post-treatment period.
[b] Two patients discontinued from the study after completing the treatment period, and one patient discontinued the study drug and discontinued from the study during the treatment period.
Source: Hezode et al.,[9] Clinical Study Report for PEARL-I.[10]

3.4 Exposure to Study Treatments

Exposure to study treatments is summarized in Table 7. In the included trial, the mean treatment duration ranged from 11.9 weeks to 12.05 weeks in all treatment groups.

TABLE 7: EXPOSURE TO STUDY INTERVENTION

	PEARL-I		
	Treatment-Naive Patients		Treatment-Experienced Patients
	OBV/PTV/RTV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks
Duration of Treatment (Days)			
Mean (SD)	83.3 (8.34)	84.4 (0.91)	84.4 (0.60)
Median (Min, Max)	84 (30, 89)	84 (83, 89)	84 (84, 86)
Duration Interval (Days)	**Discontinued Study Drug, n (%)**		
1 to 15	0	0	0
16 to 30	1 (2.3)	0	0
31 to 60	0	0	0
61 to 90	43 (97.7)	42 (100.0)	49 (100.0)

OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SD = standard deviation.
Source: Clinical Study Report for PEARL-I.[10]

3.5 Critical Appraisal

3.5.1 Internal Validity

For the treatment-naive patients, randomization and allocation concealment were well reported and shown to be effective based on equitable distribution of baseline characteristics between different treatment arms. All patients were centrally enrolled and assigned to a treatment group using the interactive response technology system.

PEARL-I was an open-label trial. 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. This may have been the case in this study, as there were more patients lost to follow-up in the OBV/PTV/RTV without RBV treatment arm whereas there were none lost to follow-up in the OBV/PTV/RTV + RBV treatment arm. Nonetheless, due to the small sample size, it is unknown if this finding is representative of the treatment or just due to small numbers skewing the results. Despite the limitations of this trial design, it is permitted by the FDA for the approval of drugs used in the treatment of CHC.[24]

Because the PEARL-I trial was uncontrolled, the efficacy of OBV/PTV/RTV with or without RBV therapy compared with existing treatments cannot be established directly from the studies. The manufacturer did not submit indirect comparisons in order to compare with other regimens. Due to these limitations, the comparative efficacy of OBV/PTV/RTV with or without RBV remains uncertain.

Due to the small number of patients enrolled in treatment groups (range 42 to 49), there were limited data on the efficacy of OBV/PTV/RTV with or without RBV in patients with genotype 4.
No sample size calculation was undertaken for patients with genotype 4 CHC infection.

3.5.2 External Validity

A considerable proportion (22%) of patients enrolled in the trial but did not enter the treatment phase. The reason was screening failures (the majority [85%] of them did not meet inclusion or exclusion criteria, and the rest were due to withdrawal of consent or other reasons). This may largely compromise the generalizability of the results on SVR to the target population. PEARL-I 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, renal insufficiency, or treatment history with DAA.

There were limited data available in patients with genotype 4 HCV. Hence, there is uncertainty about whether the SVR rates from the genotype 4 HCV population would be seen in clinical practice.

PEARL-I was an uncontrolled trial and did not compare OBV/PTV/RTV with or without RBV to other interferon-free or interferon-based regimens; thus, it is difficult to determine the place of OBV/PTV/RTV with or without RBV, relative to other regimens currently in use in Canada.

Approximately 89% of patients included in the PEARL-I trial were Caucasian, but the majority of patients who are infected with genotype 4 CHC are from North Africa. This may limit the generalizability of the results of the North African patients with genotype 4 CHC to a broader Canadian population.

Nonetheless, the clinical expert consulted on this review did not think that the response would differ based on race.

The proportion of patients included in PEARL-I with METAVIR fibrosis score in the range F0 to F1 ranged from 67.3% to 86.4%. Given that patients with METAVIR fibrosis score of ≥ F2 are more difficult to treat, this could compromise the generalizability of the results to patients with higher METAVIR fibrosis scores.

3.6 Efficacy

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

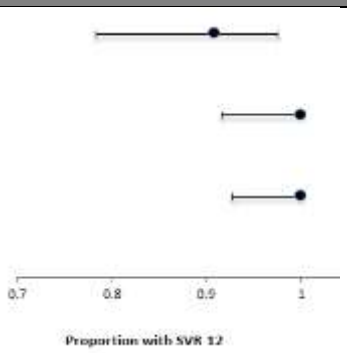
3.6.1 Sustained Virologic Response

Among the patients with genotype 4 CHC infection, SVR12 was achieved in 90.9% (95% CI, 78.3% to 97.5%) of treatment-naive patients treated with OBV/PTV/RTV without RBV, 100% (95% CI, 91.6% to 100.0%) of treatment-naive patients treated with OBV/PTV/RTV + RBV, and 100% (95% CI, 92.7% to 100.0%) of treatment-experienced patients treated with OBV/PTV/RTV + RBV (Table 8). The reasons for the four non-responses in the group of treatment-naive patients treated with OBV/PTV/RTV without RBV were on-treatment virologic failure due to rebound for one patient, relapse by post-treatment week 12 for two patients, and premature discontinuation of study drug for one patient. The SVR12 rates were calculated without imputation as a sensitivity analysis, and the results were unaffected by the missing data.

All non-cirrhotic HCV genotype 4 infected patients treated with OBV/PTV/RTV + RBV (100%) achieved SVR12, and thus the SVR12 rate did not differ across subgroups by fibrosis stage and prior treatment response (Table 10).

The unadjusted SVR12 rate in treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV without RBV was lower than the SVR12 rate in treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV + RBV by 9.09% (95% CI, 0.60% to 17.59%). When the Mantel–Haenszel method was used to adjust the comparison for differences in the proportion of IL28B CC patients (versus non-CC), the estimate of the difference increased slightly to 9.16% (95% CI, –1.29% to 19.61%); however, the width of the 95% CI increased to include 0, which would represent no statistically significant difference in SVR12 rates between the groups. However, no statistical significance does not mean no difference, especially given the small sample size and that the trial was not designed to find a statistically significant difference (Table 10).

TABLE 8: PROPORTION OF CHRONIC HEPATITIS C GENOTYPE 4 PATIENTS WHO ACHIEVED SVR12 (STUDY PEARL-I)

Population	Treatment	% SVR12 (95% CI)	
G4 naïve	OBV/PTV/RTV 12 weeks	90.9% (78.3% to 97.5%)	
G4 naïve	OBV/PTV/RTV + RBV 12 weeks	100% (91.6% to 100.0%)	
G4 experienced	OBV/PTV/RTV + RBV 12 weeks	100% (92.7% to 100.0%)	

CI = confidence interval; G4 = genotype 4; OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SVR12 = sustained virologic response 12 weeks after the end of treatment.
Source: Hezode et al.,[9] Clinical Study Report for PEARL-I.[10]

SVR24 was achieved in 86.4% (95% CI, 72.6% to 94.8) of treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV without RBV and 97.6% (95% CI, 87.4% to 99.9%) of treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV + RBV. The SVR24 results were not summarized for treatment-experienced patients treated with OBV/PTV/RTV + RBV because this treatment group was ongoing and had not completed post-treatment week 24 at the time of the database lock (Table 10). No new relapses were observed after post-treatment week 12 for patients with data. The reasons for the six non-responses in treatment-naive patients treated with OBV/PTV/RTV without RBV were on-treatment virologic failure due to rebound for one patient, relapse by post-treatment week 12 for two patients, premature discontinuation of study drug for one patient, and missing SVR24 data for two patients. The reason for the one non-response in the group of treatment-naive patients treated with OBV/PTV/RTV + RBV was missing SVR24 data.

The unadjusted SVR24 rate in treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV without RBV was lower than the SVR24 rate in treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV + RBV by 11.26% (95% CI, 0.12% to 22.39%). When the Mantel–Haenszel method was used to adjust the comparison for differences in the proportion of IL28B CC patients (versus non-CC), the estimate of the difference increased slightly to 11.38% (95% CI, –1.12%, 23.87%); however, the width of the 95% CI increased to include 0, which would represent no statistically significant difference in SVR24 rates between the groups (Table 10).

3.6.2 Relapse and On-treatment Failure

No treatment-naive or treatment-experienced genotype 4 infected patients treated with OBV/PTV/RTV + RBV experienced virologic failure during the treatment period or experienced a relapse during the post-treatment period as of the data cut-off date. At this time, the group of treatment-naive patients treated with OBV/PTV/RTV + RBV had completed post-treatment week 24 and the group of treatment-experienced patients treated with OBV/PTV/RTV + RBV had completed post-treatment week 12. In the treatment-naive group treated with OBV/PTV/RTV without RBV, one of the 44 patients experienced on-treatment virologic failure and two patients relapsed within 12 weeks post-treatment (one relapse occurred within four weeks post-treatment).

No new relapses were observed after post-treatment week 12 for patients with data.

3.6.3 Quality of Life

Table 11, Table 12, and Table 13 summarize the results for HRQoL measures.

a) Hepatitis C Virus Patient-Reported Outcome Instrument

HCV-PRO scores showed mean changes from baseline ranging from 1.48 points to 7.53 points at final on-treatment visit. The mean changes from baseline were statistically significantly lower in the OBV/PTV/RTV + RBV group than in the OBV/PTV/RTV without RBV groups at final on-treatment visit (1.48 versus 7.53, *P* = 0.016). The differences in mean changes from baseline between these two groups was not statistically significant any more at 24 weeks post-treatment (6.02 for treatment-naive patients treated with OBV/PTV/RTV + RBV versus 8.88 for treatment-naive patients treated with OBV/PTV/RTV without RBV, *P* = 0.411) (Table 11). None of the treatment groups surpassed the MCID of 10 points.

b) EQ-5D health index score

At the end of treatment, EQ-5D index scores increased 0.02 and 0.01 points from baseline in the treatment-naive patients treated with OBV/PTV/RTV without RBV and OBV/PTV/RTV + RBV, respectively, while it was decreased by 0.02 in treatment-experienced patients treated with OBV/PTV/RTV + RBV (Table 12). The differences between groups of treatment-naive patients treated with OBV/PTV/RTV without RBV and OBV/PTV/RTV + RBV in mean changes from baseline were not statistically significant at final on-treatment visit and at 24 weeks post-treatment. The MCID for the EQ-5D-5L among CHC patients remains unknown; hence no judgment can be made about whether the difference observed is clinically important or not.

c) EQ-5D visual analogue scale

At the end of treatment, the mean changes from baseline across treatment groups ranged from 3.34 to 5.36. The differences between groups of treatment-naive patients treated with OBV/PTV/RTV without RBV and OBV/PTV/RTV + RBV in mean changes from baseline were not statistically significant at final on-treatment visit and at 24 weeks post-treatment (Table 13).

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2, Methods).

3.7.1 Adverse Events

The proportion of patients who reported adverse events ranged from 87.8% to 88.1% while on OBV/PTV/RTV + RBV and was 77.3% among those who received OBV/PTV/RTV without RBV (Table 9).

3.7.2 Serious Adverse Events

Treatment-emergent serious adverse events (SAEs) were reported for one (2.3%) patient in the group of treatment-naive patients treated with OBV/PTV/RTV without RBV and no patients in the groups of treatment-naive and treatment-experienced patients treated with OBV/PTV/RTV + RBV. The SAE was a road traffic accident with contusions; this SAE resolved and was considered not related to the study drug by the investigator. In addition, this SAE did not result in discontinuation or interruption of the study drug.

3.7.3 Withdrawals Due to Adverse Events

There was no AE that resulted in discontinuation of the study drug in any of the treatment groups (Table 9).

3.7.4 Mortality

There were no deaths in any of the treatment groups (Table 9).

3.7.5 Notable Harms

Patients treated with OBV/PTV/RTV without RBV reported the occurrence of fatigue (6.8%), rash (4.5%), pruritus (14%), and nausea (9.1%). Patients treated with OBV/PTV/RTV + RBV reported the occurrence of fatigue (11.9% to 18.4%), rash (2.0% to 4.8%), pruritus (2.4% to 10.2%), and nausea (12.2% to 16.7%) (Table 9).

Three (2%) of 135 patients (one in each treatment group) had hemoglobin concentrations of 80 to < 100 g/L. Of the 91 patients who received RBV-based regimens, six (7%) had adverse events leading to RBV dose modification (three patients in each treatment group). However, only one treatment-naive patient had RBV dose reduction due to anemia; while in treatment-experienced patients, one patient had RBV dose reduction due to hemolytic anemia and two due to decreased hemoglobin. None of these adverse events required RBV dosing interruption or discontinuation. None of the events required erythropoietin or whole blood transfusion.

There was one incident of drug-induced liver injury reported in the treatment-experienced patients. This incident was a possible drug-induced liver injury with adaptation; however, the alanine aminotransferase increase was small and transient. The rise in indirect bilirubin was attributed to drug effect rather than to drug-induced liver injury. Because the rise in bilirubin precedes the rise in alanine aminotransferase, and because the bilirubin is indirect, this was not a potential Hy's law case. No other drug-induced liver injury incidents were reported.

TABLE 9: HARMS

	PEARL-I		
	Treatment-Naive Patients		Treatment-Experienced Patients
	OBV/PTV/RTV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks
N	44	42	49
Any AE	34 (77.3)	37 (88.1)	43 (87.8)
SAE	1 (2.3)	0	0
Death	0	0	0
AE leading to discontinuation of study drug	0	0	0
Common AEs[a]			
Asthenia	11 (25.0)	10 (23.8)	16 (32.7)
Diarrhea	2 (4.5)	6 (14.3)	3 (6.1)
Fatigue	3 (6.8)	5 (11.9)	9 (18.4)
Headache	13 (29.5)	14 (33.3)	14 (28.6)
Insomnia	2 (4.5)	4 (9.5)	8 (16.3)
Irritability	3 (6.8)	6 (14.3)	2 (4.1)
Myalgia	0	0	5 (10.2)

	PEARL-I		
	Treatment-Naive Patients		Treatment-Experienced Patients
	OBV/PTV/RTV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks	OBV/PTV/RTV + RBV 12 Weeks
Nasopharyngitis	2 (4.5)	2 (4.8)	6 (12.2)
Nausea	4 (9.1)	7 (16.7)	6 (12.2)
Pruritus	2 (4.5)	1 (2.4)	5 (10.2)
Notable Harms			
Rash	2 (4.5)	2 (4.8)	1 (2.0)
Fatigue	3 (6.8)	5 (11.9)	9 (18.4)
Anemia			
Hemoglobin, g/L < 100	1 (2)	1 (2)	1 (2)
Hemoglobin, g/L < 80 to 65	0	1 (2)	0
Pruritus	2 (4.5)	1 (2.4)	5 (10.2)
Nausea	4 (9.1)	7 (16.7)	6 (12.2)
Drug-induced liver injury	0	0	1 (2.0)[b]

AE = adverse event; ALT = alanine aminotransferase; OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SAE = serious adverse event.

[a] Frequency > 10%.

[b] Not a potential Hy's law case or probable relationship to study drug. Possible drug-induced liver injury with adaptation; however, the ALT increase was small (trivial) and transient. The rise in indirect bilirubin was attributed to drug effect rather than a drug-induced liver injury. Because the rise in bilirubin preceded the rise in ALT, and because the bilirubin was indirect, this was not a potential Hy's law case.

Source: Hezode et al.,[9] Clinical Study Report for PEARL-I.[10]

4. DISCUSSION

4.1 Summary of Available Evidence

One open-label trial (PEARL-I) met the inclusion criteria for this systematic review. The trial included treatment-naive and PR treatment-experienced genotype 4 CHC patients who were non-cirrhotic. The trial evaluated 12-week treatment with OBV/PTV/RTV with or without weight-based RBV. The main outcome in the included trial was the proportion of patients achieving SVR12. Key limitations included the lack of an active treatment comparator arm consisting of an existing treatment regimen for CHC genotype 4 infection. Limited data were available due to the small sample size.

4.2 Interpretation of Results

4.2.1 Efficacy

The manufacturer is seeking listing for OBV/PTV/RTV + RBV for the treatment of adults with genotype 4 CHC infection without cirrhosis who either are treatment-naive or were previously treated with PR. The listing criteria reflects the Health Canada–approved indication and the most recent Canadian guidelines.[15,17] In patient group input received by CDR for this submission, patients' expectations about treatment were to cure the infection and to provide alternative options for those patients who did not respond to or could not tolerate previous therapies. (See APPENDIX 1 for a patient input summary.)

In non-cirrhotic patients infected with genotype 4 CHC, the Health Canada–approved regimen of OBV/PTV/RTV + RBV resulted in high rates of successful treatment in treatment-naive and treatment-experienced patients (100% of patients achieving SVR12). Health Canada indicated that treatment-naive patients who cannot take or tolerate RBV may consider OBV/PTV/RTV without RBV for 12 weeks.[17] The regimen of OBV/PTV/RTV without RBV was associated with lower rates of successful treatment in treatment-naive patients (90.9%). In addition, the unadjusted SVR12 rate in treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV without RBV was lower than the SVR12 rate in treatment-naive patients with genotype 4 CHC infection treated with OBV/PTV/RTV + RBV (-9.09%; [95% CI, 0.60% to 17.59%]). When the Mantel–Haenszel method was used (the planned analysis) to adjust the comparison for differences in the proportion of IL28B CC patients (versus non-CC), the estimate of the difference increased slightly (-9.16%; [95% CI, –1.29% to 19.61%]); however, the width of the 95% CI increased to include 0, which represents no statistically significant difference in SVR12 rates between the groups. The lack of statistical significance may not mean that there was no difference, especially given that the trial was not designed to find statistically significant differences. This difference in response between treatment-naive patients who received OBV/PTV/RTV + RBV versus those who received OBV/PTV/RTV without RBV indicates that OBV/PTV/RTV + RBV is more effective in the treatment of genotype 4 patients (in those without contraindications to RBV) when compared with OBV/PTV/RTV without RBV. It must be noted; however, that the primary planned and adjusted analysis failed to find a statistically significant difference, so these results must be interpreted with caution. It is also worth noting that the study design was modified in order to not open enrolment for the group of treatment-experienced genotype 4 CHC patients to be treated with OBV/PTV/RTV without RBV. This decision was made after the review of available data at post-treatment week 4 for treatment-naive genotype 4 CHC patients from the PEARL-I study, in which none of 10 treatment-naive genotype 4 CHC patients completing treatment with OBV/PTV/RTV + RBV experienced virologic failures, but two of 10 treatment-naive genotype 4 CHC patients who received OBV/PTV/RTV without RBV experienced virologic failure. All non-cirrhotic HCV genotype 4 infected patients treated with OBV/PTV/RTV + RBV (100%) achieved SVR12, and thus the SVR12 rate did not differ across subgroups by fibrosis stage and prior treatment response. However, the proportion of patients included in PEARL-I with a METAVIR

fibrosis score in the range F0 to F1 ranged from 67.3% to 86.4%. Because patients with a METAVIR fibrosis score of ≥ F2 are harder to treat, this may compromise the generalizability of the results to patients with such METAVIR fibrosis scores. In addition, the number of patients included in each subgroup of METAVIR fibrosis scores is small (nine and 16 patients with METAVIR fibrosis score of ≥ F2 were included in treatment-naive and treatment-experienced patients treated with OBV/PTV/RTV + RBV, respectively). On the other hand, of the included patients with previous exposure to PR, 46.9% were null responders to this treatment; these patients are usually harder to treat, and the SVR12 was 100% in this subgroup of patients when treated with OBV/PTV/RTV + RBV.

Patients co-infected with HIV were excluded from the trial; hence, the efficacy of OBV/PTV/RTV + RBV is not established in patients co-infected with HIV. The Health Canada product monograph noted that the RTV component of OBV/PTV/RTV is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. It is recommended that any HCV/HIV-1 co-infected patients treated with OBV/PTV/RTV should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance. Drug interactions should be taken into account when treating HIV co-infection.

The CDR review protocol also included subgroups by ineligibility to receive PR or DAA therapy, hepatitis B co-infection, renal insufficiency, and liver transplant; however, such subgroup analyses were not undertaken because patients who would fall into each of these subgroups, except for the ineligibility to receive PR, were excluded from the trial. Hence, the efficacy of OBV/PTV/RTV + RBV in these subgroups of patients is still unknown.

Three treatment-naive patients who received OBV/PTV/RTV without RBV had virologic failure: one patient had virologic breakthrough at treatment week 8, and two patients relapsed before post-treatment week 12. All three patients had resistance-associated variants present at the time of failure that were not present at baseline. The predominant variants in NS3 and NS5A were D168V and L28S or L28V, respectively. No new relapses were observed after post-treatment week 12 for patients with data. There was no relapse or virologic failure reported in the treatment groups of OBV/PTV/RTV + RBV.

Patient group input emphasized the impact that CHC infection has on patients' quality of life. The trials of OBV/PTV/RTV with or without RBV evaluated HRQoL using one generic instrument, namely the EQ-5D, and one HCV-specific instrument, HCV-PRO. HCV-PRO appears to be a validated instrument that demonstrates convergent validity with other instruments such as the 36-Item Short Form Health Survey Physical Component Summary and Mental Component Summary scores and the EQ-VAS. Overall, there were no statistically significant differences between the treatment arms of treatment-naive patients except for the HCV-PRO at final on-treatment visit (where the mean changes from baseline were statistically significantly lower in the OBV/PTV/RTV + RBV group than the OBV/PTV/RTV without RBV group), and HRQoL did not deteriorate significantly through treatment, unlike what is typically seen with HRQoL scores from other DAA regimens that include PR,[25] which indicates that OBV/PTV/RTV with or without RBV was well tolerated. It is worth noting that all testing was exploratory and sample size was small; hence, the absence of significance difference does not indicate that there is no difference. However, in the absence of comparative HRQoL data for OBV/PTV/RTV with or without RBV with other regimens, the extent to which OBV/PTV/RTV with or without RBV is associated with improved quality of life over PR-based regimens remains uncertain.

Comparative efficacy data are limited due to the lack of an active comparator in the PEARL-I trial. The manufacturer did not provide any indirect comparisons in its submission due to difficulties with

combining data using standard methodologies. Despite the evolving standards for conducting a network meta-analysis with single-arm data, methodologies for using these data are available, and previous submissions for CHC treatments included indirect comparisons that incorporated single-arm data.[26]

CADTH recently undertook a therapeutic review that provided estimates of comparative efficacy of various treatment regimens in patients with CHC genotype 4 infection.[8] It was found that in treatment-naive patients without cirrhosis, the rate of SVR12 for the reference treatment of PR for 48 weeks was 0.65 (95% CrI, 0.63 to 0.67) and that OBV/PTV/RTV + RBV significantly increased SVR compared with PR for 48 weeks. There was no significant improvement in SVR when OBV/PTV/RTV + RBV, SOF + RBV for 24 weeks, or SOF + PR for 12 weeks were compared (SOF + RBV for 24 weeks is not a Health Canada–approved indication, while SOF + PR for 12 weeks is an approved indication for this patient population). In treatment-experienced patients, the rate of SVR12 for the reference treatment of PR for 48 weeks was 0.61 (95% CrI 0.50 to 0.73). There was no significant improvement in SVR when OBV/PTV/RTV + RBV and SOF + RBV for 24 weeks were compared (SOF + RBV for 24 weeks is not a Health Canada–approved indication for this patient population). Data were limited in the network meta-analysis to open-label, uncontrolled (or historically controlled) studies, thus limiting the ability to assess comparative efficacy using standard Bayesian indirect comparison methodologies. No individual patient data were available for analyses, so it was not possible to use comparative effectiveness methods, such as propensity scores weighting, for matching studies and identifying a comparator arm or conducting an adjusted analysis. Instead, single-arm studies were incorporated into the network meta-analysis by creating a "virtual" study where a comparator arm matched for baseline patient characteristics was identified for the single arm. Additionally, a reference comparison was sometimes not available, or the studies in the network meta-analysis were all single arm, and a reference treatment was required to statistically connect the treatments for analysis. In these cases, additional studies (meta-analyses, followed by primary observational studies if no meta-analysis data were available) were identified by clinical experts to be used to provide the required estimates. Because real-world SVR rates for the reference treatments of interest may be lower than those observed in controlled clinical trials, the use of observational study data to bring reference treatments into network meta-analyses may have biased efficacy results in favour of the DAA-containing regimens. The number of trials that contributed to some of the network meta-analyses was limited, which may have reduced the precision of the estimates from these analyses.

4.2.2 Harms

Patient group input described adverse events associated with current pegylated interferon–based therapies as severe and debilitating. Hence, it is expected that pegylated interferon–free regimens such as OBV/PTV/RTV will be better tolerated than older regimens. No control arm was included in the PEARL-I trial, and there is no direct or indirect statistical comparison available that compares harms between different regimens for the treatment of genotype 4 CHC infection; hence, it is not possible to evaluate the safety of OBV/PTV/RTV in comparison with other regimens.

Adverse events such as fatigue, headache, nausea, and rash were commonly reported; however, these events were more likely due to RBV, as seen in the PEARL-I trial that compared OBV/PTV/RTV with and without RBV. The PEARL-I trial showed that the addition of RBV to OBV/PTV/RTV was associated with higher rates of insomnia (absolute difference of 5% to 12%), nausea (3% to 8%), and fatigue (5% to 12%). It is worth noting that SAEs were relatively lower in comparison to PR-based therapies evaluated in the CADTH therapeutic review of CHC.[25] However, the relative safety of OBV/PTV/RTV with and without RBV relative to other available HCV therapies is inconclusive without a direct or indirect comparative evaluation.

Resistance emerged in three (6.8%) treatment-naive patients who received OBV/PTV/RTV without RBV; all three patients had resistance-associated variants present at the time of failure that were not present at baseline. The predominant variants in NS3 and NS5A were D168V and L28S or L28V, respectively. At present there are no clear data to support how to re-treat patients who fail treatment with OBV/PTV/RTV.

Health Canada issued an information update indicating the risk of serious liver injury associated with hepatitis C treatments OBV/PTV/RTV and OBV/PTV/RTV with dasabuvir.[27] This update indicated that international safety data have reported that cases of serious liver injury (such as hepatic failure, including cases that resulted in liver transplantation or death) have been reported in patients treated with OBV/PTV/RTV, and OBV/PTV/RTV and dasabuvir. Most patients with these serious outcomes had evidence of advanced liver disease (cirrhosis) before initiating therapy. Health Canada indicated that Holkira Pak and Technivie should not be used in patients with severe hepatic impairment (Child-Pugh Class C) or moderate hepatic impairment (Child-Pugh Class B).[27] While PEARL-I excluded patients with cirrhosis, it is worth noting that one incident of possible drug-induced liver injury with adaptation was reported in the treatment-experienced patients in the PEARL-I trial; however, this incident was not a potential Hy's law case. No other drug-induced liver injury incidents were reported.

PEARL-I trial was 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.

4.3 Potential Place in Therapy[1]

The majority of people in Canada with HCV have genotype 1, 2, or 3. Genotype 4 accounts for less than 1% of the overall HCV patients in Canada. However, much higher proportions of genotype 4 are present in centres with a high immigrant population from North Africa, the Arabian Peninsula, and some regions in the Mediterranean.

The therapy for the genotype 4 patient has been an area of unmet medical need. At present, other Health Canada–approved regimens for genotype 4 include PR for 48 weeks, and SOF + PR for 12 weeks.[19] These regimens are not preferred as they contain pegylated interferon and as such are not well tolerated. This CADTH review has noted the increased efficacy of OBV/PTV/RTV + RBV compared with PR for 48 weeks and similar efficacy to the SOF + PR 12-week regimen. In the genotype 4 non-cirrhotic patient, the non-interferon combination of OBV/PTV/RTV + RBV offers an SVR of 100% (albeit in clinical trials) in the treatment-naive and treatment-experienced patient.

The PEARL-1 study included people predominantly with F0 to F1 fibrosis (67% to 86%). Further, in the treatment-naive arm without RBV, after two patients had a virologic failure (one breakthrough and one relapse), the study was amended such that all treatment-experienced patients received RBV in combination with OBV/PTV/RTV. Therefore, the optimal regimen for treatment-naive and treatment-experienced patients without cirrhosis is OBV/PTV/RTV + RBV for 12 weeks; in this cohort, the regimen achieved an SVR of 100% in 42 treatment-naive and 49 treatment-experienced patients. It should be noted that at present this regimen is not indicated for those patients who have CHC genotype 4 with cirrhosis.

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

The combination of OBV/PTV/RTV + RBV is well tolerated; no patients were discontinued due to adverse events.[9] The regimen does require RTV "boosting"; therefore, clinicians should consider potential drug–drug interactions.

5. CONCLUSIONS

One pivotal open-label trial (PEARL-I) was included in this review. High rates of SVR12 were observed in treatment-naive and PR treatment-experienced genotype 4 CHC patients who were non-cirrhotic when OBV/PTV/RTV + RBV was administered. These SVR12 rates were higher than the SVR12 rates usually observed with PR treatment; however, PEARL-I did not include any control or active comparator arm and any comparisons are limited to indirect comparisons included in the CADTH Therapeutic Review report. HRQoL measures showed clinically insignificant changes from baseline, and differences between treatment groups were inconsistent between the different HRQoL measures. Characteristic adverse events associated with pegylated interferon appeared to occur less frequently among patients treated with OBV/PTV/RTV + RBV. The data from the PEARL-I trial were limited, due to the small numbers of patients treated.

APPENDIX 1: PATIENT INPUT SUMMARY

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

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

The Canadian Liver Foundation is the largest community organization dedicated to reducing the incidence and impact of liver disease for Canadians living with or at risk of liver disease. The Canadian Liver Foundation has received unrestricted educational grants and/or has worked on joint initiatives with AbbVie Corporation, Astellas Pharma Canada, Inc., Boehringer Ingelheim (Canada) Ltd., Gilead Sciences Canada Inc., Janssen Inc., Merck Canada Inc., Novartis Pharmaceuticals Canada Inc., and Hoffmann-La Roche Ltd. In addition, Dr. Sherman, Chairperson of the Canadian Liver Foundation, has received honoraria from AbbVie Corporation, Boehringer Ingelheim (Canada) Ltd., Merck Canada Inc., Janssen Inc., Hoffmann-La Roche Ltd., Gilead Sciences Canada Inc., Vertex Pharmaceuticals, and Bristol-Myers Squibb.

The Canadian Treatment Action Group (CTAC) is Canada's national non-governmental organization addressing access to treatment, care, and support for people living with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). CTAC's organizational goals are focused on working with relevant stakeholders to identify, develop, and implement policy and program solutions. CTAC received unrestricted organizational and/or educational grants from the following organizations in the 2014-2015 fiscal year: Abbott/AbbVie Corporation, Gilead Sciences Canada Inc., Janssen Inc., and ViiV Healthcare.

The Pacific Hepatitis C Network's mission is to strengthen the capacity of individuals and organizations throughout British Columbia to prevent new HCV infections and to improve the health and treatment outcomes of people already living with HCV. The Pacific Hepatitis C Network has received one-time project grants from AbbVie Corporation, Bristol-Myers Squibb, Gilead Sciences Canada Inc., Janssen Inc., and Merck Canada Inc. for the Hepatitis C Treatment Information Project, an online HCV treatment

information resource. The Pacific Hepatitis C Network declares no conflicts of interest in the preparation of this submission.

The 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, and general hepatitis information and encourages testing among at-risk groups. The HepCBC Hepatitis C Education & Prevention Society has received funding for hepatitis C–oriented projects such as publishing educational materials, organizing educational forums, attending and presenting at educational conferences, advertising in newspapers and on buses (events and hepatitis C patient awareness), and holding awareness activities from the following pharmaceutical companies over the last four years: Merck Canada Inc., Hoffman-La Roche Ltd., Vertex Pharmaceuticals, Gilead Sciences Canada Inc., Janssen Inc., Bristol-Myers Squibb, Boehringer Ingelheim (Canada) Ltd., and AbbVie Corporation, plus support from Rx&D, the pharmaceutical umbrella organization.

2. Condition-Related Information

The information provided in all remaining sections was gathered via online surveys, monthly support meetings, an organization volunteer, and a webinar that included patients diagnosed with HCV, caregivers, and health care professionals.

Hepatitis C 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, diarrhea, loss of appetite, headaches, disrupted sleep, and slower motor reflexes. In some patients, the disease affects their cognitive functions, where their concentration or attention span, speed of thought, fluency of speech, learning, and memory are affected. The fatigue and other symptoms may be severe and can limit patients' ability to work, manage their home, care for family members, and maintain friendships.

Patients must cope with the stigma associated with HCV and are often reluctant to disclose their HCV status for fear of rejection, discrimination, or ostracism. The social stigma, fear of spreading the infection, and the uncertainty regarding their future health exact a high emotional toll on patients that may lead to depression, anxiety, loss of hope, and social isolation. To patients, a cure means a return to normal life — the ability to work full-time, think clearly, and have intimate contact with others — and no more worries about dying decades too soon.

Among the different HCV genotypes, genotype 4 is relatively rare, with less than 2% of individuals with HCV in Canada having genotype 4 HCV. Genotype 4 HCV is much more common in the Middle East and Africa, and it was noted that with increased global migration and "compassionate migration," for example, with the current Syrian refugee crisis, the prevalence of genotype 4 HCV will likely increase in Canada.

3. Current Therapy-Related Information

The currently available treatment options for genotype 4 HCV are limited, and include pegylated interferon alfa with ribavarin (PR), or sofosbuvir in combination with pegylated interferon alfa and ribavirin. Genotype 4 patients, depending upon their insurance coverage or the reimbursement criteria in their province, are primarily eligible for treatment with dual therapy with PR. Dual therapy involves weekly injections of interferon and six to eight ribavirin pills per day for 24 to 48 weeks. Interferon has well-documented and often significant side effects. These side effects include anemia, sleep loss,

depression, mood swings, joint pain, rashes, hearing loss, skin sores, hair loss, headaches, chills, nausea, severe fatigue, and excessive weight loss, and additional medications are often required to manage the side effects associated with interferon. In addition, many patients are unable to take interferon-based therapy due to contraindications. It was noted that dual therapy with PR yields success rates of only 43% to 70% for a 48-week course of treatment.

For caregivers and health professionals, the challenges of caring for and achieving a cure for patients with HCV are significant. Patients require a great deal of education and counselling about treatment options, and if they decide to undergo treatment, it can require additional tests, lab results, forms, and appeal letters before patients can actually access the therapies they need.

4. Expectations About the Drug Being Reviewed

Respondents were encouraged about the availability of this agent because of its associated frequency of sustained virologic response of 91% to 100%, because of the limited treatment options currently available for those with genotype 4 HCV, and because it does not need to be used with interferon. The ability to avoid the use of interferon was noted as a "game changer" for some patients, particularly those with contraindications to interferon who therefore were unable to receive treatment for HCV genotype 4. However, some patients were concerned about the need for using ribavirin in combination with ombitasvir/paritaprevir/ritonavir. Several patients noted that they were discouraged from seeking treatment because of continued presence of ribavirin in contemporary therapy options. In addition, one group noted that the FDA had recently approved the use of ombitasvir/paritaprevir/ritonavir with or without ribavirin, and these people were hopeful that this approval would translate to a similar approval status and use in Canada.

5. Additional Information

Patients are concerned that the prices of these drugs will be so high that CADTH (and/or provincial Pharmacare plans) will either not approve the treatment at all, or implement coverage criteria that require patients to undergo and fail very challenging standard treatments (with both interferon and ribavirin) before having access to ombitasvir/paritaprevir/ritonavir. Delaying treatment until liver disease is more advanced has an impact on patients' physical and mental well-being. It is frustrating for individuals, especially those who are experiencing multiple barriers, to be told that they are not sick enough to qualify for treatment. Patients worry about the liver damage that may be caused by delaying treatment. The sooner a person is effectively treated (i.e., cured), the less chance they have of inadvertently infecting someone else. Improved treatments for HCV have the potential to reduce social system and health care costs for patients with severe liver disease. 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. As a result, patients would prefer that this treatment is offered to all people with HCV, regardless of the patient's severity of liver damage.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 5, 2015
Alerts:	Weekly search updates until February 17, 2016
Study Types:	No search filters were applied
Limits:	No language or date limits 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
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
.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	(Technivie* or viekirax* or Viekira or vikera pak* or vikerapak* or Viekirapak* or Viekira pak*).ti,ab,ot,kw,hw,rn,nm.
2	S900007110.rn,nm.
3	(OBV adj2 PTV).ti,ab,ot,kw,hw,rn,nm.

MULTI-DATABASE STRATEGY	
#	**Searches**
4	"ABT-450/r/ABT-267".ti,ab,ot,kw,hw,rn,nm.
5	1 or 2 or 3 or 4
6	(Ombitasvir or abt267* or abt 267*).ti,ab,ot,kw,hw,rn,nm.
7	(1258226-87-7 or 1444832-14-7).rn,nm.
8	6 or 7
9	(Paritaprevir or abt 450* or abt450* or veruprevir).ti,ab,ot,kw,hw,rn,nm.
10	1221573-85-8.rn,nm.
11	9 or 10
12	(Ritonavir or ritona-vir or a 84538 or a84538 or abt 538 or abt538 or abt 84538 or abt84538 or norvir or ritovir or RTV or TMC114r or TMC-114r or Abbott 84538 or HSDB-7160 or HSDB7160 or DRG-0244 or DRG0244).ti,ab,ot,kw,hw,rn,nm.
13	155213-67-5.rn,nm.
14	12 or 13
15	8 and 11
16	8 and 14
17	15 or 16
18	5 or 17
19	18 use pmez
20	(Technivie* or viekirax* or Viekira or vikera pak* or vikerapak* or Viekirapak* or Viekira pak*).ti,ab.
21	(OBV adj2 PTV).ti,ab.
22	"ABT-450/r/ABT-267".ti,ab.
23	20 or 21 or 22
24	*ombitasvir/ or (Ombitasvir or abt267* or abt 267*).ti,ab.
25	*paritaprevir/ or (Paritaprevir or abt 450* or abt450* or veruprevir).ti,ab.
26	*ritonavir/ or (Ritonavir or ritona-vir or a 84538 or a84538 or abt 538 or abt538 or abt 84538 or abt84538 or norvir or ritovir or RTV or TMC114r or TMC-114r or Abbott 84538 or HSDB-7160 or HSDB7160 or DRG-0244 or DRG0244).ti,ab.
27	24 and 25
28	24 and 26
29	27 or 28
30	23 or 29
31	30 use oemezd
32	exp animals/
33	exp animal experimentation/ or exp animal experiment/
34	exp models animal/
35	nonhuman/
36	exp vertebrate/ or exp vertebrates/
37	animal.po.
38	or/32-37
39	exp humans/
40	exp human experimentation/ or exp human experiment/
41	human.po.
42	or/39-41

MULTI-DATABASE STRATEGY	
#	**Searches**
43	38 not 42
44	31 not 43
45	44 not conference abstract.pt.
46	remove duplicates from 45

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:	September 30, 2015
Keywords:	Drug name, Indication
Limits:	No language or date 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

No studies excluded.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 10: EFFICACY OUTCOMES

Outcome/Subgroup	PEARL-I					
	Treatment-Naive Patients				Treatment-Experienced Patients	
	OBV/PTV/RTV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
SVR12[a]	40/44	90.9% (78.3 to 97.5)[b]	42/42	100% (91.6 to 100.0)[b]	49/49	100% (92.7 to 100.0)[b]
Unadjusted difference,[b] % (95% CI)	–9.09% (–17.59 to –0.60)					
Stratum-adjusted difference,[c] % (95% CI)	–9.16% (–19.61 to 1.29)					
SVR24[d]	38/44[e]	86.4% (72.6 to 94.8)[b]	41/42[f]	97.6% (87.4 to 99.9)[b]	NR	NR
Unadjusted difference,[b] % (95% CI)	–11.26% (–22.39 to –0.12)					
Stratum-adjusted difference,[c] % (95% CI)	–11.38% (–23.87 to 1.12)					
SVR12 by Fibrosis Stage						
F0 to F1	NR	NR	33/33	100%	33/33	100%
F2	NR	NR	6/6	100%	11/11	100%
F3	NR	NR	2/2	100%	5/5	100%
F4	NR	NR	1/1	100%	0	
SVR12 by Prior Treatment Response						
Null responder	NA	NA	NA	NA	23/23	100.0 (85.2 to 100.0)
Partial responder	NA	NA	NA	NA	9/9	100.0 (66.4 to 100.0)
Relapser	NA	NA	NA	NA	17/17	100.0 (80.5 to 100.0)
On-Treatment Virologic Failure	1/44	2.3%	0	0%	0	0%
Relapse	2/42	4.8%	0	0%	0	0%

CI = confidence interval; HCV = hepatitis C virus; IL28B = interleukin 28B genotype; LLOQ = lower limit of quantification; NA = not applicable; NR = not reported; OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SVR = sustained virologic response; SVR12/24 = sustained virologic response 12 or 24 weeks after the end of treatment.

[a] SVR12 = HCV RNA < LLOQ in the SVR12 window (12 weeks after last actual dose of study drug) without any confirmed quantifiable post-treatment value before or during that SVR window.

[b] CI constructed using the Clopper-Pearson exact method.

[c] Difference in rates after adjusting for IL28 genotype (CC or non-CC) using stratum-adjusted Mantel–Haenszel proportions and continuity-corrected variances.

[d] SVR24 = HCV RNA < LLOQ in the SVR24 window (12 weeks after last actual dose of study drug) without any confirmed quantifiable post-treatment value before or during that SVR window.

[e] Two patients had missing SVR24 data.

[f] One patient had missing SVR24 data.

Source: Hezode et al.,[9] Clinical Study Report for PEARL-I.[10]

TABLE 11: SUMMARY OF HEPATITIS C VIRUS PATIENT-REPORTED OUTCOMES

Outcome / Subgroup	PEARL-I					
	Treatment-Naive Patients				Treatment-Experienced Patients	
	OBV/PTV/RTV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks	
	N	Mean (SD)	n	Mean (SD)	n	Mean (SD)
On-Treatment						
Baseline	42	79.98	42	81.52	46	72.76
Change from baseline at week 2	42	2.13 (7.933)	42	–0.71 (7.819)	46	3.67 (12.162)
Change from baseline at week 4	42	5.59 (8.099)	42	–0.60 (11.265)	46	4.25 (12.790)
Change from baseline at week 8	43	5.61 (9.007)	41	0.91 (12.755)	46	3.95 (15.524)
Change from baseline at week 12	41	7.17 (7.409)	39	0.43 (13.554)	46	7.07 (18.369)
Change from baseline at final on-treatment visit	43	7.53 (7.430)	42	1.48 (14.097)	46	7.07 (18.369)
LS Mean Difference (SE) (95% CI) ***P* value**[a]	5.46 (2.214) (1.06 to 9.86) 0.016					
Post-Treatment						
Change from baseline at week 4	43	7.75 (7.191)	41	3.63 (15.837)	46	11.31 (14.196)
Change from baseline at week 24	40	8.88 (7.929)	41	6.02 (15.249)	NR	NR
LS Mean Difference (SE) (95% CI) ***P* value**[a]	1.94 (2.346) (–2.73 to 6.61) 0.411					

ANCOVA = analysis of covariance; CI = confidence interval; HCV = hepatitis C virus; HCV-PRO = HCV Patient-Reported Outcomes; LS = least squares; NR = not reported; OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SD = standard deviation; SE = standard error.

Note: The HCV-PRO total score ranges from 0 to 100 with a higher score being desirable.

[a] LS mean, 95% CI, and *P* value from ANCOVA model with treatment group as a factor and baseline score as a covariate.

Source: Clinical Study Report for PEARL-I.[10]

TABLE 12: SUMMARY OF EQ-5D-5L HEALTH INDEX SCORE

Outcome / Subgroup	PEARL-I					
	Treatment-Naive Patients				Treatment-Experienced Patients	
	OBV/PTV/RTV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
On-Treatment						
Baseline	42	0.87	42	0.88	46	0.88
Change from baseline at	42	0.01 (0.083)	42	0.00 (0.113)	46	–0.04 (0.122)

Outcome / Subgroup	PEARL-I					
	Treatment-Naive Patients				Treatment-Experienced Patients	
	OBV/PTV/RTV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
week 2						
Change from baseline at week 4	42	0.02 (0.107)	42	0.02 (0.109)	46	–0.05 (0.128)
Change from baseline at week 8	43	0.01 (0.096)	41	0.01 (0.137)	46	–0.05 (0.127)
Change from baseline at week 12	41	0.02 (0.102)	39	0.01 (0.128)	46	–0.02 (0.125)
Change from baseline at final on-treatment visit	43	0.02 (0.100)	42	0.01 (0.125)	46	–0.02 (0.125)
LS Mean Difference (SE) (95% CI) ***P* value**[a]	0.01 (0.022) (–0.04 to 0.05) 0.817					
Post-Treatment						
Change from baseline at week 4	43	–0.00 (0.148)	41	0.02 (0.156)	46	–0.00 (0.099)
Change from baseline at week 24	40	0.03 (0.107)	41	0.06 (0.109)	NR	NR
LS Mean Difference (SE) (95% CI) ***P* value**[a]	–0.03 (0.023) (–0.08 to 0.01) 0.156					

ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels Questionnaire; LS = least squares; NR = not reported; OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SD = standard deviation; SE = standard error.
Note: The EQ-5D-5L index scores range from 0 to 1 (higher score is desirable), reflecting the societal perspectives on a certain health state.
[b] LS mean, 95% CI, and *P* value from ANCOVA model with treatment group as a factor and baseline score as a covariate.
Source: Clinical Study Report for PEARL-I.[10]

TABLE 13: SUMMARY OF EQ-5D VISUAL ANALOGUE SCALE

Outcome / Subgroup	PEARL-I					
	Treatment-Naive Patients				Treatment-Experienced Patients	
	OBV/PTV/RTV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
On-Treatment						
Baseline	42	77.26	42	78.31	47	74.68
Change from baseline at week 2	42	0.24 (7.237)	42	1.17 (13.244)	47	2.13 (16.140)
Change from baseline at week 4	42	1.90 (9.028)	42	1.12 (15.878)	47	2.23 (16.638)

Outcome / Subgroup	PEARL-I					
	Treatment-Naive Patients				Treatment-Experienced Patients	
	OBV/PTV/RTV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks		OBV/PTV/RTV + RBV 12 Weeks	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Change from baseline at week 8	43	2.60 (7.820)	41	3.66 (13.937)	47	1.36 (18.686)
Change from baseline at week 12	41	3.41 (9.479)	39	5.38 (16.850)	47	3.34 (16.991)
Change from baseline at final on-treatment visit	43	3.49 (9.257)	42	5.36 (16.260)	47	3.34 (16.991)
LS Mean Difference (SE) (95% CI) ***P* value**[a]	–2.10 (2.446) (–6.96 to 2.77) 0.393					
Post-Treatment						
Change from baseline at week 4	43	2.51 (7.762)	41	5.71 (17.167)	47	7.62 (15.959)
Change from baseline at week 24	40	6.13 (9.216)	41	6.29 (16.922)	NR	NR
LS Mean Difference (SE) (95% CI) ***P* value**[a]	–1.05 (2.652) (–6.33 to 4.23) 0.693					

ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-5L VAS = EuroQol 5-Dimensions 5-Level visual analogue scale; LS = least squares; NR = not reported; OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SD = standard deviation; SE = standard error; VAS = visual analogue scale.
Note: The EQ-5D-5L VAS score ranges from 0 to 100, where 0 = worst imaginable health state and 100 = best imaginable health state.
[a] LS mean, 95% CI, and *P* value from ANCOVA model with treatment group as a factor and baseline score as a covariate.
Source: Clinical Study Report for PEARL-I.[10]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Sustained virologic response (SVR) at 12 weeks (SVR12) as a surrogate for SVR at 24 weeks (SVR24)
- EuroQol 5-Dimensions Questionnaire (EQ-5D)
- Hepatitis C Virus Patient-Reported Outcomes (HCV-PRO) instrument.

Findings

SVR12 and SVR24

SVR24 is the standard primary end point for assessing response to agents that treat chronic hepatitis C (CHC) infection.[28] 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.[28] The authors reviewed data submitted to the FDA (2002 to 2011) from 15 phase 2 and phase 3 studies that included various treatment durations of pegylated interferon alfa-2a, pegylated interferon alfa-2b, albinterferon alfa-2b, telaprevir, and boceprevir. The majority of the 13,599 participants were genotype 1 (N = 11,730), while 69 patients had genotype 4. In addition to assessing SVR12, the authors also reviewed the predictive value of SVR4 with respect to SVR24.

SVR12 was achieved by 51.8% (7,051 of 13,599 patients) and SVR24 by 50.6% (6,881 of 13,599 patients) of adults in the database.[28] The positive predictive value between SVR12 and SVR24 was 98.3% and the negative predictive value was 98.8%. Thus, 1.2% of patients would be falsely identified as not achieving SVR if an outcome of SVR12 was adopted over SVR24, and 1.7% of patients would be falsely identified as having a sustained undetectable viral load. The authors attributed the latter to relapse, reinfection, or "other" reasons. Results were consistent across the 15 studies, with between 0% and 4.3% of patients achieving SVR12 but not SVR24. Older studies that used HCV 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 chronic hepatitis C (CHC) treatments.[28] They also stated that these conclusions should be applied with caution to direct-acting antiviral (DAA)–only regimens, considering that they were based on data from regimens containing interferon plus ribavirin.[28] 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.[29] This study included 781 patients with CHC; all had received pegylated interferon plus ribavirin (RBV) (PR). Among the 781 individuals, 74 patients had genotype 4 or 5 CHC (genotype 4 was not reported separately from genotype 5). Of the 781 patients, 573 had an end-of-treatment response and were thus included in the analysis. Of the 409 patients who had an SVR12, 408 went on to have an SVR24.[29] Therefore, this study also demonstrated a high concordance between achievement of SVR12 and eventual achievement of SVR24. The authors concluded that SVR12 is as informative as SVR24 when assessing SVR. This study used the transcription-mediated amplification assay, which is a newer, more sensitive assay.

Another study explored differences between SVR12 and SVR24 among treatment-naive genotype 1 CHC patients who received PR.[30] The authors pooled single-arm data for pegylated interferon alfa 2a or alfa 2b plus RBV from 35 clinical trials. Of these trials, only one study reported both SVR12 and SVR24. The proportion with an SVR12 or SVR24 was pooled across trials using a DerSimonian-Laird random effects

model. Data for SVR12, SVR24, and each type of pegylated interferon were pooled separately. The authors also performed a Bayesian random effects meta-regression of the proportion with SVR12 or SVR24, controlling for the type of pegylated interferon. The authors concluded that SVR12 was 5% to 6% higher than SVR24, although the credible intervals (CrIs) overlapped in the conventional meta-analysis, and in the Bayesian meta-regression the CrIs included the null value (SVR12 versus SVR24 relative risk 1.13; 95% CrI, 0.99 to 1.26).[30] These findings should be interpreted with caution considering that they were based on single treatment group data. Naive pooling of single-arm data is not an acceptable method to determine comparative efficacy as it ignores the benefits of randomization and may therefore be subject to the same biases as a comparison of independent cohort studies. In addition, the analysis was limited to data from patients who received PR and did not examine the concordance of SVR12 and SVR24 among those who received a DAA regimen.

One study performed an analysis of the concordance between SVR12 and SVR24 using pooled data from phase 3 clinical trials of sofosbuvir-containing regimens (NEUTRINO, FISSION, POSITRON, FUSION, and VALENCE).[31] From this analysis, a total of 777 of 779 patients (99.7%) who achieved SVR12 also achieved SVR24, including all patients (n = 296) with hepatocellular carcinoma genotype 1 or 4 to 6, all patients (n = 270) with genotype 2, and 211 or 213 patients (99.0%) with genotype 3. Thus the negative predictive value measuring concordance between SVR12 and SVR24 was 100%, and the positive predictive value was 99.7%.

EQ-5D

The EQ-5D is a generic health-related quality of life instrument that may be applied to a wide range of health conditions and treatments.[32,33] The first of two parts of the EQ-5D comprise a descriptive system that classifies respondents (aged 12 years or older) based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, 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, corresponding with 243 different health states. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[32,33] 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 for the 3L version (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 minimal clinically importance differences (MCIDs) for the 3L version of the scale have ranged from 0.033 to 0.074.[34]

The investigators of the included study in this review used the EQ-5D-5L version. This version of the descriptive system consists of the same five dimensions as the standard version (EQ-5D-3L), but includes five response levels instead of three: "no problems," "slight problems," "moderate problems," "severe problems," and "unable to do/extreme problems" for all dimensions.[35] There are 3,125 possible health states associated with the 5L version of the EQ-5D. The validity of the 5L version was compared with the standard version among patients with chronic hepatic diseases (n = 1,088), among whom 31.8% had CHC.[35] Overall, in comparison with the standard version, the 5L version appeared to be more feasible (0.8% versus 8.5% of patients returned blank questionnaires). The overall proportion of inconsistent responses between the two versions was 2.9%, similar to the minimum possible value (1.12%). The proportion of respondents answering "11111" was 39.4% with the standard version and 36.4% with the 5L system, indicating an absolute reduction of 2.9% and a relative reduction of 7.5% of the ceiling effect on the full profile. The correlation coefficient between 5L and VAS was moderate to high, ranging from –0.39 for self-care to a maximum of −0.55 for usual activities. There were no relevant differences in correlations between individual dimensions and the VAS between the standard and 5L versions. Other psychometric properties such as responsiveness and reliability were not assessed. The MCID for the EQ-5D-5L among CHC patients remains unknown.

HCV-PRO Instrument

The HCV-PRO has been developed specifically to capture the function and well-being impact of HCV conditions and treatment upon function and well-being as related to physical, emotional, and social health, productivity, intimacy, and perceptions of overall quality of life in adults.[36] The HCV-PRO contains 16 items with five levels of response choices, corresponding to "all of the time" (1) to "none of the time" (5). The HCV-PRO total score is the sum of 16 individual item scores converted to a 0 to 100 scale as follows: ([sum − 16] × 100) / 64.[37] A higher HCV-PRO score indicates a better state of health. Psychometric testing for the HCV-PRO was conducted among members of the online Harris International Panel (n = 241), who self-reported past, current, or previous treatment for HCV. The HCV-PRO demonstrated internal consistency reliability with a Cronbach's alpha exceeding 0.97 for the total score. Convergent validity was established as Pearson's product-moment correlation coefficients for the HCV-PRO total score with the 36-Item Short Form Health Survey (SF-36) scale scores ranging from 0.52 (general health) to 0.84 (role physical). There was a correlation of HCV-PRO total score with the HCV symptoms checklist (r = –0.87) such that a higher symptom burden was associated with reduced function and well-being on the HCV-PRO. Discriminant validity was established as HCV-PRO scores differentiated between currently treated patients, those previously treated, and patients never treated (P < 0.01). In a separate study among CHC patients (n = 74),[38] HCV-infected patients received DAAs for 12 weeks with PR for 48 weeks or placebo plus PR. Correlations (0.64 to 0.96) between HCV-PRO total scores, SF-36 Physical Component Summary and Mental Component Summary (PCS/MCS) scores, and EQ-VAS scores at all time points supported convergent validity. Using effect size and receiver-operating characteristic curve analyses (HCV-PRO response versus SF-36 PCS/MCS and EQ-VAS minimally important difference [MID] thresholds), an MCID of –10 points was reported.[37]

Summary

- A review using individual patient data from 15 phase 2 and phase 3 studies (N = 13,599 participants), in which the majority were patients with genotype 1 CHC (N = 11,730), suggests that SVR12 is a reliable surrogate for SVR24. The authors suggest that SVR12 may become a new definition for SVR for regulatory approval.
- The generic EQ-5D health-related quality of life instrument has been widely used, but has not been properly validated in CHC. Among patients with chronic hepatic diseases, the EQ-5D-5L version

appears to be more feasible and consistent and to have a lower ceiling effect in comparison with the standard version. The MCID for the EQ-5D-5L among CHC patients remains unknown.

- The HCV-PRO is a health-related quality of life instrument specific to patients with CHC. The HCV-PRO has demonstrated convergent validity with other instruments such as the SF-36 PCS/MCS scores, and EQ-VAS. The HCV-PRO has also demonstrated low ceiling and floor effects and high internal consistency reliability. The reported MCID is –10 points.

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