Common Drug Review
Clinical Review Report

June 2015

Drug	ombitasvir, paritaprevir, ritonavir and dasabuvir (Holkira Pak)
Indication	For the treatment of adults with genotype 1 chronic hepatitis C virus (HCV) infection, including those with compensated cirrhosis.
Listing request	For the treatment of adults with genotype 1 chronic hepatitis C (CHC) infection, including patients who are treatment-naive or who have failed previous therapies against HCV, and patients with compensated cirrhosis.
Manufacturer	AbbVie Corporation

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ABBREVIATIONS

3-D	combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir)
AE	adverse event
ART	antiretroviral therapy
CHC	chronic hepatitis C
CI	confidence interval
DAA	direct-acting antiviral drug
DB	double-blind
DSV	dasabuvir
EQ-5D	EuroQol 5-Dimensions Questionnaire
EQ VAS	EuroQol visual analogue scale
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV-PRO	Hepatitis C Virus Patient-Reported Outcomes Instrument
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
INF	interferon
ITT	intention-to-treat
LDV	ledipasvir
LLOQ	lower limit of quantification
MCID	minimal clinically important difference
OBV/PTV/RTV	ombitasvir/paritaprevir/ritonavir
OL	open-label
PBO	placebo
Peg-IFN	pegylated interferon
PR	pegylated interferon and ribavirin
PTV	paritaprevir
RBV	ribavirin
RCT	randomized controlled trial
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SE	standard error
SD	standard deviation
SF-36	Short-Form 36-Item Health Survey
SF-36 MCS	Short-Form 36-Item Health Survey mental component summary

SF-36 PCS	Short-Form 36-Item Health Survey physical component summary
SIM	simeprevir
SOF	sofosbuvir
SVR	sustained virologic response
SVR12	sustained virologic response for 12 consecutive weeks
SVR24	sustained virologic response for 24 consecutive weeks
TEL	telaprevir

EXECUTIVE SUMMARY

Introduction

In Canada, approximately 242,000 Canadians are infected with hepatitis C virus (HCV), although it is believed there are a number of infected individuals who are unaware that they have HCV. In 2009, there were more than 11,000 incident cases of HCV infection, mostly due to injection drug use. Of those infected, approximately 25 % will clear their infection spontaneously, and the remainder will develop chronic hepatitis C (CHC) infection. Current therapy for CHC consists of direct-acting antiviral agents (DAAs) used in combination with pegylated interferon (Peg-IFN) and ribavirin (RBV) for up to 48 weeks, which are quickly being replaced by interferon (IFN)-free regimens as the standard of care, due to improved efficacy and safety profiles. The combination of ledipasvir and sofosbuvir (LDV/SOF) is an oral once-daily IFN-free regimen approved for use in CHC genotype 1 infection, given for eight to 24 weeks, and associated with high (> 90%) sustained virologic response (SVR) rates for 12 weeks following treatment (SVR12) and an improved adverse effect profile compared with pegylated interferon and ribavirin (PR)-based regimens.

The objective of this systematic review is to evaluate the efficacy and safety of ombitasvir (OMB), paritaprevir (PAR), ritonavir (RTV) and dasabuvir (DAS), or OBV/PTV/RTV and DSV, with or without ribavirin (RBV) for the treatment of genotype 1 CHC infection.

Indication under review
For the treatment of adults with genotype 1 chronic HCV infection, including those with compensated cirrhosis.
Listing criteria requested by sponsor
For the treatment of genotype 1 CHC infection, including patients who are treatment-naive or who have failed previous therapies against HCV, and patients with compensated cirrhosis.

Results and Interpretation

Included Studies

Six trials met the inclusion criteria for this systematic review. Three double-blind (DB) trials included patients with no previous experience with antiviral treatment for HCV (SAPPHIRE I [N = 631], PEARL III [N = 419], and PEARL IV [N = 305]); two trials included patients who failed previous antiviral treatment (SAPPHIRE II [DB; N = 395] and PEARL II [open-label (OL); N = 389]), and one trial included both treatment-naive and treatment-experienced patients who had hepatic cirrhosis (TURQUOISE II [OL; N = 381]). The trials evaluated 12-week treatment with OBV/PTV/RTV and DSV plus RBV relative to OBV/PTV/RTV and DSV alone (three trials) or OBV/PTV/RTV and DSV plus RBV administered for 24 weeks (TURQUOISE II).

The primary efficacy outcome measure was the proportion of patients achieving SVR12. The SVR12 rate was compared with a historical comparison base rate from older PR and telaprevir (TEL) trials. For treatment-naive patients, the historical control rates used were 72%, 80%, and 78% for genotype 1a patients, genotype 1b patients, and cirrhosis-free patients, respectively. For treatment-experienced patients, rates varied according to the response to previous treatment; the population-based weighted average ranged from 59% for patients with genotype 1a to 71% for those infected with genotype 1b. Other outcomes included relapse rate and health-related quality of life (HRQoL).

The main limitation of the included trials was the lack of a treatment group consisting of an existing treatment regimen for CHC genotype 1 infection. Comparison to a historical control could be biased due to differences in the distribution of potential confounders of effect. Despite the scientific limitations associated with historical control study designs, these designs were considered adequate by Health Canada and the FDA to grant regulatory approval.

Efficacy

The proportion of patients achieving SVR12 ranged from 86% to 100% in all treatment groups. These response rates were statistically superior to the historical comparator. OBV/PTV/RTV and DSV plus RBV was compared with OBV/PTV/RTV and DSV in three trials; PEARL II and PEARL III showed that the differences between the two interventions were not statistically significant, while PEARL IV showed that OBV/PTV/RTV and DSV plus RBV was associated with a statistically significant higher proportion of patients achieving SVR12 (97% versus 90.2% without RBV [absolute risk difference: 6.8%; 95% CI, 1.5% to 12.0%]). Treatment of cirrhotic patients with 24 weeks of OBV/PTV/RTV and DSV was associated with a numerically higher proportion of patients achieving SVR12 than the 12-week treatment (95.9% versus 91.8%), but the difference was not statistically significant.

Relapses were limited to 38 cases, and did not show an association of their occurrence with any particular patient characteristics or treatment group.

The included trials evaluated HRQoL using three instruments: the Short-Form 36-Item Health Survey (SF-36), the EuroQol 5-Dimensions Instrument (EQ-5D) and the Hepatitis C Virus Patient-Reported Outcomes Instrument (HCV-PRO), which is an HCV-specific HRQoL instrument. In general, there were no statistically significant differences between treatment groups within each trial, and even if one instrument showed a difference in one trial, this difference was not consistent with the other instruments. It should be noted that while no clinically meaningful changes occurred during treatment, there was also no substantive deterioration in HRQoL scores during treatment.

A total of two deaths were reported in the included trials: one in SAPPHIRE I, and one in TURQUOISE II. Both cases were reported in the OBV/PTV/RTV and DSV plus RBV groups.

Despite the absence of direct comparative trials of OBV/PTV/RTV and DSV, with or without RBV and other treatments for CHC infection, no indirect comparisons were submitted by the manufacturer or identified in the literature.

Harms

Adverse events were frequent across all treatment groups in the included trials, ranging from 67% to 92%. OBV/PTV/RTV and DSV plus RBV was associated with a higher rate of adverse events than the placebo groups in SAPPHIRE I (87.5% versus 73.4%) and SAPPHIRE II (91.2% versus 82.5%). The use of OBV/PTV/RTV and DSV with RBV was also associated with a higher rate of adverse events than when the combination was used without RBV alone in PEARL III (80.0% versus 67.0%) and PEARL IV (92.0% versus 82.4%); however, PEARL II showed similar rates for the two groups (79.1% versus 77.9%). Adverse events leading to drug discontinuation were relatively rare (≤ 2.3%) in all treatment groups. The rates of serious adverse events (SAEs) ranged from 0% to 6.3% across treatment groups in the included studies; cirrhotic patients in TURQUOISE II reported the highest rate of SAEs. Cirrhotic patients in TURQUOISE II reported the highest rate of SAEs (6.3% versus 4.7% for the 12- and 24-week treatments, respectively).

Other Considerations

One trial that evaluated OBV/PTV/RTV and DSV plus RBV in patients co-infected with human immunodeficiency virus (HIV) did not meet inclusion criteria for the review, as it was a pilot phase 2 trial. The trial randomized 63 patients into 12- and 24-week treatments with OBV/PTV/RTV and DSV plus RBV. SVR12 rates of 93.5% and 90.6% were reported for the two groups, respectively.

Conclusions

Six pivotal trials were included in this review. OBV/PTV/RTV and DSV administered according to the Health Canada–approved regimen was associated with high rates of SVR12 in patients with genotype 1 CHC infection, in both treatment-naive and treatment-experienced patients. TheSVR12 rates were higher than those reported for the historical comparator rate derived from previous TEL and PR trials. HRQoL measures showed clinically insignificant changes from baseline, and differences between treatment groups in each trial were inconsistent between the different HRQoL measures.

SAEs and withdrawals due to adverse events were infrequent. Characteristic adverse events associated with Peg-IFN appeared to occur less frequently among patients treated with OBV/PTV/RTV and DSV. However, the relative efficacy and safety of OBV/PTV/RTV and DSV compared with more recent IFN-free HCV therapies is uncertain due to the absence of direct or indirect comparative evaluations.

TABLE 1: SUMMARY OF RESULTS

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I		PEARL III		PEARL IV		SAPPHIRE II		PEARL II		TURQUOISE II	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 88)	OBV/PTV/ RTV&DSV - RBV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/RTV &DSV + RBV 24 Weeks (n = 172)
SVR12 (ITT Population)												
N (%) [95% CI]	455 (96.2) [94.5 to 97.9]	NR	209 (99.5) [98.6 to 100]	207 (99.0) [97.7 to 100]	97 (97.0) [93.7 to 100]	185 (90.2) [86.2 to 94.3]	286 (96.3) [94.1 to 98.4]	NR	85 (96.6) [92.8 to 100]	91 (100) [95.9 to 100]	191 (91.8) [87.6 to 96.1]	165 (95.9) [92.6 to 99.3]
Difference (95% CI)	NR		–0.5 (–2.1 to 1.1)		–6.8 (–12.0 to –1.5)		NR		3.4 (–0.4 to 7.2)		–4.18 (–9.79 to 1.42)	
Relapse at week 12 post-treatment, N (%)												
n/N (%)	7 (1.5)	NR	0	0	1 (1.0)	10 (5.2)	7 (2.4)	NR	0	0	12 (5.9)	1 (0.6)
SF-36 PCS, mean (SD) change from baseline												
Baseline	52.0	49.3	52.3	52.5	50.9	49.9	50.8	50.8	52.0	51.1	48.1	47.6
Final	–1.3 (7.9)	0.7 (7.0)	–0.5 (6.8)	–0.1 (6.7)	–0.6 (7.2)	0.9	–2.8 (7.7)	–1.3 (6.3)	–2.1 (6.1)	–0.5 (5.9)	–1.1 (6.76)	–1.5 (6.8)
Difference (SE)	–0.93 (0.64); *P* = 0.147		–0.56 (0.59); *P* = 0.346		–1.32 (0.82); *P* = 0.109		–1.53 (0.80); *P* = 0.058		1.32 (0.85); *P* = 0.121		–0.56 (0.67); *P* = 0.401	
SF-36 MCS, mean (SD) change from baseline												
Baseline	49.8	49.9	50.9	50.8	51.8	48.3	50.1	48.5	47.0	49.6	48.6	47.1
Final	–3.7 (10.5)	–2.0 (9.9)	–1.4 (9.2)	–0.1 (9.1)	–2.9 (10.6)	0.3 (10.1)	–3.7 (9.7)	–0.6 (9.0)	–2.4 (8.4)	0.1 (8.5)	–2.3 (9.4)	–2.9 (10.5)
Difference (SE)	–1.73 (0.92) ; *P* = 0.062		–1.17 (0.81) ; *P* = 0.150		–2.3 (1.22); *P* = 0.060		–2.71 (1.07); *P* = 0.012		–2.81 (1.21); *P* = 0.022		–1.03 (0.99); *P* = 0.296	
EQ-5D health index score												
Baseline	0.88	0.85	0.89	0.89	0.88	0.85	0.87	0.86	0.88	0.86	0.84	0.81
Final	–0.02 (0.1)	–0.01 (0.1)	0.0 (0.12)	0.01 (0.1)	–0.04 (0.1)	–0.00 (0.1)	–0.04 (0.2)	–0.02 (0.2)	–0.02 (0.1)	0.00 (0.1)	–0.03 (0.1)	–0.02 (0.1)
Difference (SE)	–0.001 (0.011); *P* = 0.961		–0.002 (0.012); *P* = 0.836		–0.028 (0.014); *P* = 0.052		–0.025 (0.016); *P* = 0.114		0.014 (0.015); *P* = 0.372		0.01 (0.014); *P* = 0.701	
EQ VAS score, mean (SD)												
Baseline	81.2	78.9	82.5	83.7	82.6	80.3	79.0	78.6	79.3	79.1	76.1	73.0
Final	–0.6 (15.2)	–0.3 (14.1)	2.3 (13.4)	1.4 (13.3)	–0.0 (13.2)	3.5 (13.3)	–1.6 (15.1)	–1.1 (13. 6)	–0.2 (12.3)	3.4 (12.1)	0.8 (15.8)	0.6 (16.8)

	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I		PEARL III		PEARL IV		SAPPHIRE II		PEARL II		TURQUOISE II	
Outcome	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 88)	OBV/PTV/ RTV&DSV - RBV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/RTV &DSV + RBV 24 Weeks (n = 172)
Difference (SE)	0.60 (1.3); *P* = 0.633		0.25 (1.14); *P* = 0.825		–2.73 (1.49); *P* = 0.068		–0.37 (1.6); *P* = 0.820		3.48 (1.72); *P* = 0.044		–1.47 (1.504); *P* = 0.330	
HCV-PRO score, mean (SD)												
Baseline	79.5	77.3	81.1	82.9	80.8	76.5	77.4	78.1	77.2	77.3	74.4	70.5
Final	–4.8 (17.0)	–0.6 (14.5)	0.4 (16.7)	0.3 (15.0)	–3.3 (15.3)	1.9 (15.6)	–4.4 (16.5)	–0.9 (11.6)	–1.6 (14.6)	1.5 (13.4)	–1.8 (14.9)	–2.0 (16.2)
Difference (SE)	–3.61 (1.44); *P* = 0.012		–0.51 (1.43); *P* = 0.723		–4.31 (1.84); *P* = 0.020		–3.85 (1.74); *P* = 0.028		3.19 (2.04); *P* = 0.120		–1.1 (1.6); *P* = 0.466	
AEs	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	24 weeks
Any AE	**414 (87.5)**	**116 (73.4)**	**168 (80.0)**	**140 (67.0)**	**92 (92.0)**	**169 (82.4)**	**271 (91.2)**	**80 (82.5)**	**72 (79.1)**	**74 (77.9)**	**191 (91.8)**	**156 (90.7)**
SAEs	**10 (2.1)**	**0**	**4 (1.9)**	**4 (1.9)**	**3 (3.0)**	**1 (0.5)**	**6 (2.0)**	**1 (1.0)**	**2 (2.2)**	**2 (2.1)**	**13 (6.3)**	**8 (4.7)**
Discontinuation due to AEs	**3 (0.6)**	**1 (0.6)**	**0**	**0**	**0**	**2 (1.0)**	**3 (1.0)**	**0**	**2 (2.2)**	**0**	**4 (1.9)**	**4 (2.3)**

AE = adverse event; CI = confidence interval; DB = double-blind; EQ-5D = EuroQol 5-Dimensions Questionnaire; EQ VAS = EuroQol visual analogue scale; ITT = intention-to-treat; HCV-PRO = Hepatitis C Virus Patient-Reported Outcomes Instrument; MCS = mental component summary; NR = not reported; OBV/PTV/RTV&DSV = ombitasvir/paritaprevir/ritonavir and dasabuvir); OL = open-label; PBO = placebo; PCS = physical component summary; SAE = serious adverse event; SD = standard deviation; SE = standard error; SF-36 = Short-Form 36-Item Health Survey; SVR12 = sustained virologic response for 12 consecutive weeks; RBV = ribavirin.
Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hepatitis C virus (HCV) infection is a global health problem, with more than 170 million individuals chronically infected worldwide. In Canada, approximately 242,000 Canadians are infected with HCV, although it is believed there are a number of infected individuals who are unaware that they have HCV. In 2009, there were more than 11,000 incident cases of HCV infection, mostly due to injection drug use.[7] Of those infected, approximately 25 % will clear infection spontaneously (range 15% to 45%) and the remainder will develop chronic hepatitis C (CHC) infection.[8,9] There are six genotypes of HCV, and although treatment strategies tend to differ depending on genotype, there is no clear evidence that genotype affects disease severity. Genotype 1 infections account for most HCV infections in Canadians (55% to 65%).[10-12] Genotypes 2 and 3 are the next most common and are estimated to comprise 14% and 20% of HCV infections in Canada, respectively, according to a recent review.[13]

In patients with CHC, 15% to 25% will develop progressive liver disease, end-stage liver disease, or hepatocellular carcinoma, or ultimately will be candidates for liver transplantation.[14,15] Male gender, alcohol use, human immunodeficiency virus (HIV) co-infection, obesity, and increasing age are associated with an increased risk of liver disease progression. HIV co-infection is reported in 17 % of patients with HCV infection in Canada.[16] While incident cases of HCV in North America and Canada[17,18] continue to decline, it is expected that liver-related morbidity and mortality will continue to increase over the coming decades, as those who are already infected age.[15]

1.2 Standards of Therapy

Before 2011, pegylated interferon and ribavirin (PR) therapy was the gold standard for patients with CHC infection. Approximately half of patients with genotype 1 CHC, the most prevalent type of CHC infection in Canada, could expect to achieve sustained virologic response (SVR) with a 48-week course of PR treattment. Tolerability of PR-based regimens has been a significant limitation to their use. The addition of direct-acting antivirals (DAAs) to PR resulted in a further advance in SVR rates as compared with PR-regimens that did not include a DAA. Currently, there are three DAAs available in Canada for use in conjunction with PR for the treatment of genotype 1 CHC infection. These include the protease inhibitors, boceprevir and simeprevir (SIM), and sofosbuvir (SOF), which targets HCV polymerase. Telaprevir (TEL), another protease inhibitor used in conjunction with PR, has recently been discontinued.

Drug development for the treatment of CHC has been rapid and paradigm shifting in the past few years. The standard of care for CHC genotype 1 infection has now become the first available interferon (IFN)-free regimen of ledipasvir (LDV) and SOF (LDV/SOF) as an oral fixed-dose combination pill administered once daily for eight to 24 weeks (Table 2).[19] This regimen offers the advantages of improved tolerability and improved efficacy over PR-based regimens. The available evidence from three open-label phase 3 clinical trials indicates that SVR was achieved by more than 90% of patients who received LDV/SOF for eight, 12, or 24 weeks.[19]

1.3 Drug

Holkira Pak is a combination of ombitasvir (OMB), paritaprevir (PTV), ritonavir (RTV), and dasabuvir (DAS) or OBV/PTV/RTV and DSV as detailed in Table 3. OBV/PTV/RTV and DAS is composed of two tablets: the first is composed of 12.5 mg OMB, 75 mg PTV, and 50 mg RTV. The second tablet is composed of 250 mg DAS. The recommended dosage is two tablets daily of the combination tablet (OMB/PTV/RTV) and two tablets daily of DAS (Table 2). RBV is indicated with OBV/PTV/RTV and DAS in non-cirrhotic patients with genotype 1a infection, and in patients with compensated cirrhosis.

TABLE 2: DOSING REGIMEN FOR HOLKIRA PAK

Patient Population	Treatment Composition	Dosage	Duration
HCV genotype 1a, without cirrhosis	OBV/PTV/RTV DAS + RBV	25 mg/150 mg/100 mg once daily 250 mg twice daily < 75 kg = 1,000 mg; ≥ 75 kg = 1,200 mg	12 weeks
HCV genotype 1b, without cirrhosis	OBV/PTV/RTV DAS	25 mg/150 mg/100 mg once daily 250 mg twice daily	
HCV genotype 1a and 1b, with cirrhosis	OBV/PTV/RTV DAS + RBV	25 mg/150 mg/100 mg once daily 250 mg twice daily < 75 kg = 1,000 mg; ≥ 75 kg = 1,200 mg	

DAS = dasabuvir; HCV = hepatitis C virus; OBV/PTV/RTV = ombitasvir, paritaprevir, ritonavir; RBV = ribavarin

Indication under review
For the treatment of adults with genotype 1 chronic HCV infection, including those with compensated cirrhosis.
Listing criteria requested by sponsor
For the treatment of genotype 1 CHC infection, including patients who are treatment-naive or who have failed previous therapies against HCV, and patients with compensated cirrhosis.

TABLE 3: KEY CHARACTERISTICS OF OMBITASVIR, PARITAPREVIR, RITONAVIR, AND DASABUVIR

	Ombitasvir	Paritaprevir	Ritonavir	Dasabuvir	Sofosbuvir/ Ledipasvir	Ribavirin
Mechanism of Action	Inhibition of HCV NS5A	Inhibition of HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins)	Pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure	Non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene	Both SOF and LDV target the HCV NS5B and NS5A proteins, respectively	The mechanism of action is not fully understood; it likely involves the direct inhibition of HCV replication, the inhibition of inosine monophosphate dehydrogenase, the induction of mutagenesis, and immunomodulation
Indication	Only available in OBV/PTV/RTV and DSV combination		Treatment of HIV infection when therapy is warranted	Only available in OBV/PTV/RTV and DSV combination	Treatment of CHC genotype 1 infection in adults	Indicated in combination with other drugs for the treatment of CHC in adults
Route of Administration	Oral					
Recommended Dose	25 mg once daily (included in the combination tablet)	150 mg once daily (included in the combination tablet)	100 mg once daily (included in the combination tablet)	250 mg twice daily (morning and evening)	90 mg/400 mg LDV/SOF once daily	Dosage is based on patient's weight: < 75 kg = 1,000 mg ≥ 75 kg = 1,200 mg
Serious Side Effects/Safety Issues	When used in the combination therapy: fatigue, nausea, asthenia, and headache		Diarrhea, nausea, vomiting, anorexia, abdominal pain (upper and lower), paresthesia and oral paresthesia, and fatigue or asthenia	When used in the combination therapy: fatigue, nausea, asthenia, and headache	Headache and fatigue	RBV/SOF: fatigue and headache. RBV/Peg-IFN alpha/SOF: fatigue, anemia, neutropenia, insomnia, headache, and nausea

CHC = chronic hepatitis C virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDV = ledipasvir; OBV/PTV/RTV and DSV = ombitasvir/paritaprevir/ritonavir and dasabuvir; peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of the combination of OBV, PTV, RTV, and DAS for the treatment of CHC genotype 1 infection in adults.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other phase 3 studies were selected for inclusion based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with CHC genotype 1 infection **Subpopulations of interest:** • Treatment history (treatment-naive, prior relapse, prior partial response, null response) with PR, DAA plus PR therapy, or LDV/SOF • Fibrosis level • HIV co-infection • Genotype subtype • Renal insufficiency • Post-liver transplant • Cirrhosis • Decompensated liver disease
Intervention	OBV/PTV/RTV 25 mg/150 mg/100 mg once daily, and DSV 250 mg twice daily with or without RBV
Comparators	• LDV/SOF • PBO in combination with PR • boceprevir in combination with PR • TEL in combination with PR • SIM in combination with PR • SOF in combination with PR • PBO or no treatment
Outcomes	**Key efficacy outcomes:** • SVR • Relapse • HRQoL • Mortality (all cause and liver-related) **Other efficacy outcomes:** • Hepatic-related morbidity outcomes (e.g., histological changes, hepatocellular carcinoma, liver failure, liver transplant) **Harms outcomes:** • SAE, WDAE, AE • Harms of special interest: rash, fatigue, anemia, neutropenia, pruritus, depression, sleep loss, nausea, photosensitivity
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; CHC = chronic hepatitis C; DAA = direct-acting antiviral drug; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; LDV = ledipasvir; OBV/PTV/RTV and DSV = ombitasvir, paritaprevir, ritonavir and dasabuvir; PBO = placebo; PR = pegylated interferon and ribavirin; RBV = ribavirin; RCT = randomized controlled trial; SAE = serious adverse event; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; WDAE = withdrawal due to adverse events.

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

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

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

The initial search was completed on January 21, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on May 20, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), and Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers, and through contact with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons for exclusion) are presented in Appendix 3.

3. RESULTS

3.1 Findings from the Literature

A total of six trials were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

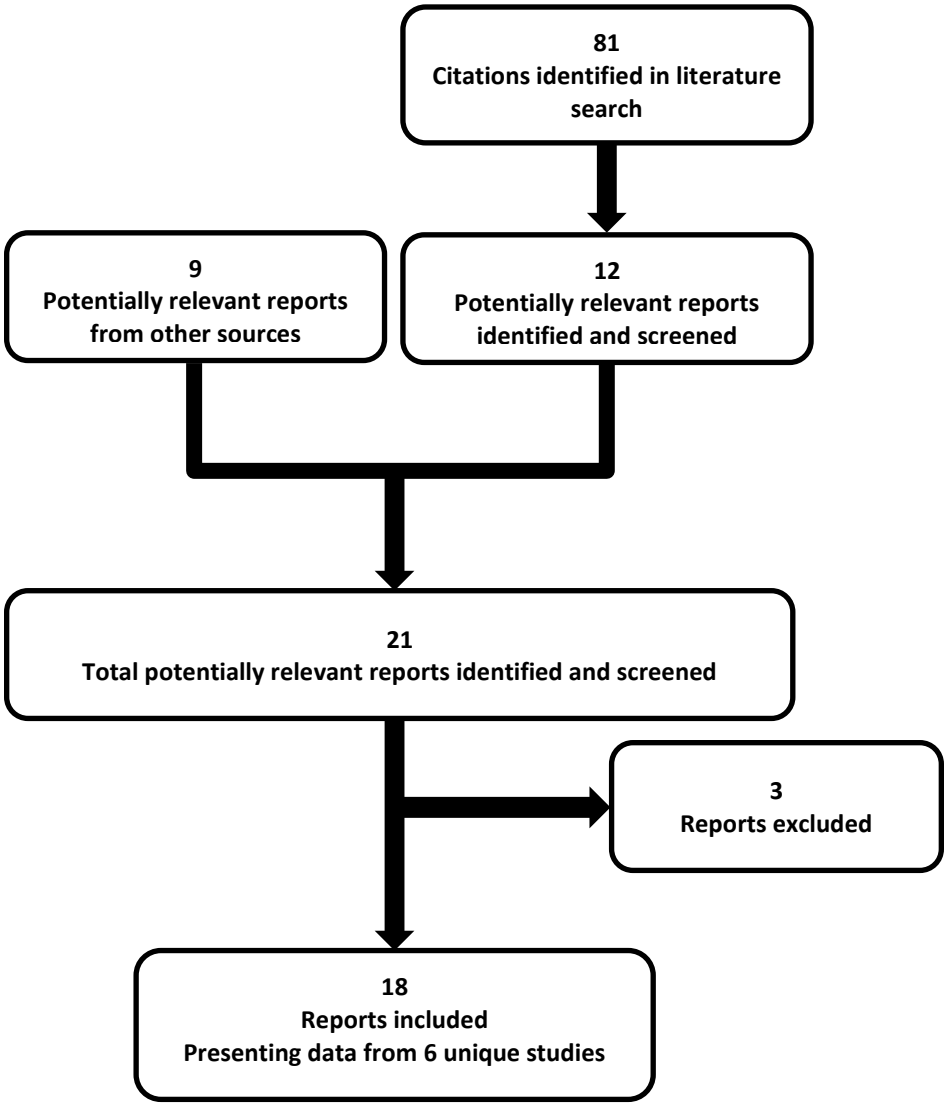

TABLE 5: DETAILS OF INCLUDED STUDIES

		Treatment-Naive Patients			Treatment-Experienced Patients		Mixed-Experience
		SAPPHIRE I (M11-646)	PEARL III (M13-961)	PEARL IV (M14-002)	SAPPHIRE II (M13-098)	PEARL II (M13-389)	TURQUOISE II (M13-099)
DESIGNS & POPULATIONS	**Study design**	DB, placebo-controlled RCT	DB, active-controlled RCT		DB, placebo-controlled RCT	Open-label, active-controlled RCT	
	Locations	Australia, Canada, US, Western Europe	Europe, Israel, and US	Canada, UK, and US	Australia, Canada, Europe, Russia, and US	US, Western Europe, and Turkey	Australia, Canada, US, and Western Europe
	Randomized (N)	631	419	305	395	187	381
	Inclusion criteria	Adult patients					
		No cirrhosis					Compensated cirrhosis
		No previous antiviral treatment for HCV			Failure to previous PR treatment[a]		Either treatment-naive or PR-experienced
		• HCV genotype 1	• HCV genotype 1b	• HCV genotype 1a	• HCV genotype 1	• HCV genotype 1b	• HCV genotype 1
	Exclusion criteria	• Co-infection with other HCV genotypes • Positive tests for HBsAg or anti-HIV Ab		• Uncontrolled seizures • Uncontrolled diabetes	• Anemia, thrombocytopenia, neutropenia • Creatinine clearance < 60 mL/min		
DRUGS	**Intervention**	12 weeks of treatment with the combination of two tablets per day of 12.5 mg OBV, 75 mg PTV, and 50 mg RTV; two tablets per day of 250 mg DSV; and RBV (weight-based dosing)[b]					
	Comparator(s)	Placebo	The intervention regimen with a placebo replacing RBV		Placebo	The intervention without RBV	Intervention regimen for 24 weeks
		Historical comparator (TEL + PR)					
DURATION	Screening	Up to 35 days					
	DB	12 weeks				NA	
	Follow-up	48 weeks					72 weeks
OUTCOMESYY	**Primary end point**	SVR12 versus historical comparator					SVR12 (12 vs. 24 weeks)
		NIM = 64%	NIM = 73%	NIM = 65%	NIM = 64%		
	Other end points	ALT normalization rate	Percentage of patients with hemoglobin < LLN	Percentage of patients with hemoglobin < LLN	ALT normalization rate	Percentage of patients with hemoglobin < LLN	Percentage of patients with SVR12 in the 24-week group compared with the 12-week group

		Treatment-Naive Patients			Treatment-Experienced Patients		Mixed-Experience
		SAPPHIRE I (M11-646)	PEARL III (M13-961)	PEARL IV (M14-002)	SAPPHIRE II (M13-098)	PEARL II (M13-389)	TURQUOISE II (M13-099)
	Publications	Feld et al. (2014)[20,21]	Ferenci et al. (2014)[22,23]		Zeusem et al. (2014)[24,25]	Andreone et al. (2014)[26]	Poordad et al. (2014)[27,28]

Ab = antibodies; DB = double-blind; DSV = dasabuvir; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LLN = lower limit of normal; NA = not applicable; NIM = non-inferiority margin; OBV = ombitasvir; PR = pegylated interferon and ribavirin; PTV = paritaprevir; RBV = ribavirin; RCT = randomized controlled trial; RTV = ritonavir; SVR12 = sustained virologic response for 12 consecutive weeks; TEL = telaprevir.

[a] Failure defined as null responders, non-responders or partial responders, or relapsers.

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

Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

3.2 Included Studies

3.2.1 Description of Studies

Six pivotal phase 3 multi-centre randomized controlled trials (RCTs) were included in this systematic review (Table 5). Despite the fact that these were controlled trials, only one trial (TURQUOISE II) conducted statistical comparisons between trial groups, while all other trials compared the active treatment groups with a historical comparator in terms of the main outcome: sustained virologic response for 12 consecutive weeks (SVR12). Three trials included treatment-naive patients (SAPPHIRE I, PEARL III, and PEARL IV), two trials included treatment-experienced patients (SAPPHIRE II and PEARL II), and one trial included patients with mixed-treatment experience (TURQUOISE II). The included trials evaluated 12-week treatments with the following: OBV/PTV/RTV and DSV plus RBV versus placebo (SAPPHIRE I and SAPPHIRE II); versus OBV/PTV/RTV and DSV with RBV -placebo (PEARL III and PEARL IV); versus OBV/PTV/RTV and DSV without placebo (PEARL II); and versus a 24-week course of OBV/PTV/RTV and DSV plus RBV (TURQUOISE II).

The primary objectives of the included trials, except TURQUOISE II, were to evaluate the safety and to show the non-inferiority, in terms of SVR12 response rate, of OBV/PTV/RTV and DSV co-administered with RBV to the historical comparator of TEL + PR. SVR12 rate for the historical comparator was calculated from the pivotal trials of TEL + PR (Table 7). The primary objectives of TURQUOISE II were to assess the safety and to compare the efficacy, in terms of SVR12 response rate, of OBV/PTV/RTV and DSV co-administered with RBV, when given for 12 weeks compared with 24 weeks.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The main inclusion and exclusion criteria for the included trials are summarized in Table 5.

The included trials recruited adult patients with CHC infection. CHC infection was defined by either testing positive for anti-HCV antibody (Ab) or HCV ribonucleic acid (RNA) at least six months before screening, and positive for HCV RNA and anti-HCV Ab at the time of screening; or testing positive for anti-HCV Ab and HCV RNA at the time of screening, with a liver biopsy consistent with CHC infection (or a liver biopsy performed before enrolment with evidence of CHC disease). Childbearing patients had to use two effective methods of birth control while receiving study drugs, and for seven months after stopping study drugs. The included patients had to be free from hepatic cirrhosis at screening in all trials except in TURQUOISE II, which exclusively included patients with compensated hepatic cirrhosis. 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 virus (HBV) or HIV co-infection, uncontrolled seizures, uncontrolled diabetes, a creatinine clearance < 60 mL/min, anemia, thrombocytopenia, or neutropenia at baseline.

SAPPHIRE II and PEARL II exclusively enrolled patients who had previous PR treatment, and trial TURQUOISE II included a mix of patients who had prior experience with PR treatment and those who were treatment-naive. The three trials required that patients who had previous experience with PR to have documentation that they were confirming adherence to their prior therapy. Additionally, trials SAPPHIRE II and PEARL II required that patients had failed their PR treatments. Failure was defined by one of the following categories:

- **Null responders:** received at least 12 weeks of PR for the treatment of HCV and failed to achieve a 2 log_{10} international units (IU)/mL reduction in HCV RNA at week 12. Patients were considered to

have met this definition if the lack of treatment response was documented following 10 to 16 weeks of treatment; or:

- **Non-responders or partial responders:** received at least 20 weeks of PR for the treatment of HCV and achieved ≥ 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12, but failed to achieve HCV RNA undetectable at the end of treatment. Patients were considered to have met this definition if the lack of treatment response was documented following 10 to 16 weeks of treatment; or:
- **Relapsers:** received at least 36 weeks of PR for the treatment of HCV and were undetectable at the end of treatment, although HCV RNA was detectable within 52 weeks of treatment follow-up.

b) Baseline Characteristics

Baseline characteristics for the included trials are summarized in Table 6.

Baseline characteristics were well balanced across treatment groups within each included trial. The majority of patients were male and Caucasian. In general, the mean treatment age in trials of treatment-naive patients, which tended to include younger patients was slightly lower (at 50 years) than trials of treatment-experienced patients (at 54 years), while the mixed-experienced patients in TURQUOISE II had a mean age of 57 years.

SAPPHIRE I, SAPPHIRE II, and TURQUOISE II included patients infected with HCV genotype 1; almost two-thirds of patients had genotype 1a infection. PEARL II and PEARL III only included patients infected with HCV genotype 1b infection, while PEARL IV included only patients infected with genotype 1a HCV. SAPPHIRE II, PEARL II, and TURQUOISE II included patients with previous exposure to PR; the majority of patients were non-responders to this treatment (range 35% to 50%), which was followed by relapsers (13% to 36%). Partial responders were the least represented (8% to 29%).

3.2.3 Interventions

All included trials evaluated the same test intervention that consisted of 12 weeks of treatment with the combination of two tablets per day of 12.5 mg OBV, 75 mg PTV, and 50 mg RTV; two tablets per day of 250 mg DSV; and 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.

The control intervention treatment varied across the different trials. SAPPHIRE I and SAPPHIRE II used a placebo treatment administered in a similar way as the test intervention: at the end of the double-blind period, the placebo group received the active treatment for 12 weeks. The control group in PEARL III and PEARL IV used the combination of OBV/PTV/RTV and DSV (two tablets per day of 12.5 mg OBV, 75 mg PTV, and 50 mg RTV; and two tablets per day of 250 mg DSV) and a placebo-matched RBV. PEARL II used the combination of OBV/PTV/RTV and DSV only without RBV or RBV-matched placebo. In TURQUOISE II, the control intervention consisted of the same treatment as the test intervention group, except that it was administered for 24 weeks instead of 12 weeks.

3.2.4 Outcome Measures

Outcome measures were consistent among the included trials. The primary efficacy outcome measure was the proportion of patients achieving SVR12, defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after stopping all study drugs.

Relapse was defined as having 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 completing treatment and having achieved a HCV RNA less than LLOQ at the end 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 physical and mental components of the Short-Form 36-Item Health Survey instrument (SF-36), EuroQol 5-Dimensions Questionnaire (EQ-5D), and Hepatitis C Virus Patient-Reported Outcomes Instrument (HCV-PRO). Appendix 4 summarizes the validity of these three measures in HCV patients.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS

	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002)		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 158)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV 12 Weeks (n = 95)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/ RTV&DSV + RBV 24 Weeks (n = 172)
Age, mean (SD)	49.4 (11.0)	51.2 (10.2)	48.4 (11.9)	49.2 (12)	51.6 (11.0)	51.4 (10.6)	51.7 (10.3)	54.9 (8.5)	54.2 (10.9)	54.2 (10.5)	57.1 (7.0)	56.5 (7.9)
Male, n (%)	271 (57.3)	73 (46.2)	106 (50.5)	86 (41.1)	70 (70.0)	129 (62.9)	167 (56.2)	60 (61.9)	45 (49.5)	57 (60.0)	146 (70.2)	121 (70.3)
Race, n (%)												
Caucasian	428 (90.5)	144 (91)	198 (94.3)	196 (94.2)	86 (86.0)	171 (83.4)	269 (90.6)	86 (88.7)	84 (92.3)	86 (90.5)	199 (95.7)	161 (93.6)
Black	26 (5.5)	8 (5.1)	10 (4.8)	10 (4.8)	10 (10.0)	26 (12.7)	22 (7.4)	10 (10.3)	3 (3.3)	6 (6.3)	6 (2.9)	6 (3.5)
Other	19 (2.9)	6 (3.8)	2 (1.0)	2 (1.0)	3 (3.0)	5 (2.5)	6 (2.0)	1 (1.0)	4 (4.4)	3 (3.3)	3 (1.4)	5 (2.9)
Genotype, n (%)												
HCV_1a	322 (68.1)	105 (66.5)	0	0	100 (100)	204 (99.5)	173 (58.2)	57 (58.8)	2 (2.2)	1 (1.1)	140 (67.3)	121 (70.3)
HCV_1b	151 (31.9)	53 (33.5)	210 (100)	209 (100)	0	1 (0.5)	123 (41.4)	40 (41.2)	89 (97.8)	93 (97.9)	68 (32.7)	51 (29.7)
IL28B_CC	144 (30.4)	50 (31.6)	44 (21.0)	44 (21.1)	31 (31.0)	63 (30.7)	34 (11.4)	7 (7.2)	10 (11.0)	7 (7.4)		
IL28B_CT	254 (53.7)	82 (51.9)	127 (60.5)	132 (63.2)	58 (58.0)	105 (51.2)	200 (67.3)	70 (72.2)	59 (64.8)	67 (70.5)		
IL28B_TT	75 (15.9)	26 (16.5)	39 (18.6)	33 (15.8)	11 (11.0)	37 (18.0)	63 (21.2)	63 (21.2)	22 (24.2)	21 (22.1)		
Baseline HCV RNA												
log_{10} IU/mL, mean (SD)	6.40 (0.62)	6.47 (0.65)	6.29 (0.77)	6.33 (0.67)	6.64 (0.50)	6.53 (0.68)	6.55 (0.54)	6.52 (0.48)	6.56 (0.56)	6.48 (0.53)	6.41 (0.62)	6.53 (0.52)
Prior treatment status												
Treatment-naive	473	158	210 (100)	209 (100)	100 (100)	205 (100)	0	0	0	0	86 (41.3)	74 (43.0)
Treatment-experienced	0	0	0	0	0	0	297 (100)	97 (100)	91 (100)	95 (100)	122 (58.7)	98 (57.0)
Previous response to PR treatment												

	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002)		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 158)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV 12 Weeks (n = 95)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/ RTV&DSV + RBV 24 Weeks (n = 172)
Non-responder (null responder)	NA	NA	NA	NA	NA	NA	146 (49.2)	47 (48.5)	32 (35.2)	33 (34.7)	75 (36.1)	62 (36.0)
Partial responder	NA	NA	NA	NA	NA	NA	65 (21.9)	21 (21.6)	26 (28.6)	27 (28.2)	18 (8.7)	13 (7.6)
Relapser	NA	NA	NA	NA	NA	NA	86 (29.0)	29 (29.9)	33 (36.3)	35 (36.8)	29 (13.9)	23 (13.4)
Metavir score												
F0-F1	363 (76.7)	116 (73.4)	150 (71.4)	141 (67.8)	63 (63.0)	132 (64.4)	202 (68.0)	65 (67.0)	64 (70.3)	61 (64.2)	Not reported	
F2	70 (14.8)	27 (17.1)	38 (18.1)	47 (22.6)	21 (21.0)	35 (17.1)	53 (17.8)	17 (17.5)	13 (14.3)	21 (22.1)		
≥ F3	40 (8.5)	15 (9.5)	22 (10.5)	20 (9.6)	16 (16.0)	38 (18.5)	42 (14.1)	15 (15.5)	14 (15.4)	13 (13.7)		

HCV = hepatitis C virus; NA = not applicable; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; PR = pegylated interferon and ribavirin; RBV = ribavirin; RNA = ribonucleic acid; SD = standard deviation.
Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

3.2.5 Statistical Analysis

Randomization was stratified to various patient characteristics. In SAPPHIRE I, PEARL III, and PEARL IV, randomization was stratified by IL28B genotype (CC versus non-CC); in addition, SAPPHIRE I stratified patients by HCV subtype (1a versus non-1a). PEARL II and SAPPHIRE II stratified randomization based on type of response to previous PR treatment (null responder, partial responder, or relapser); TURQUOISE II stratified the randomization by receipt of previous PR treatment (treatment-experienced) versus treatment-naive.

The primary analysis in all trials except TURQUOISE II compared SVR12 in the test intervention groups with a historical control SVR12. Data for the historical comparator control rates were taken from clinical trials evaluating treatment with TEL + PR (Table 7). According to the manufacturer's analyses, to be considered non-inferior to the historical SVR rate for TEL, a margin of 10.5% was used. Thus, non-inferiority to the historical SVR rate for TEL-based therapy was obtained by showing that the lower confidence bound (LCB) for the SVR12 rate in the current trials was greater than the upper confidence bound (UCB) of the SVR rate for the historical TEL-based therapy, minus 10.5%. For example, in the SAPPHIRE I trial that included treatment-naive patients without cirrhosis, the SVR12 rate had to be 70% in order to conclude that the test intervention is non-inferior to the historical comparator. The manufacturer did not provide any justifications for the preservation rate of 10.5%. These trials were planned to achieve at least 95% statistical power to demonstrate non-inferiority versus the historical comparator. TURQUOISE II was the only trial that included a between-group comparison for SVR12, and it compared the SVR12 rates between the 12-week and 24-week treatments. TURQUOISE II was planned to achieve 90% power to demonstrate non-inferiority, with a two-sided 97.5% LCB greater than 43%. In all trials, secondary analyses were conducted to test for the superiority of OBV/PTV/RTV and DSV, compared with the historical comparator; these analyses were only conducted if the non-inferiority was granted for OBV/PTV/RTV and DSV.

TABLE 7: SUSTAINED VIROLOGIC RESPONSE RATES FOR TELAPREVIR-BASED THERAPY

	Treatment-Naive Patients		
	ADVANCE Study[a]	ILLUMINATE Study[a]	Meta-analysis[b]
	T12/PR, n/N (%)	T12/PR, n/N (%)	T12/PR, % (95% CI)
Treatment-naive patients without cirrhosis	270/342 (79)	367/479 (77)	78 (75 to 80)
Treatment-naive genotype 1a patients	162/217 (75)	273/388 (70)	72 (68 to 75)
Treatment-naive genotype 1b patients	119/142 (84)	112/149 (75)	80 (75 to 84)
	Treatment-Experienced Patients		
	REALIZE Study[a]		
	GT1a (pooled T12/PR48), n/N (%)	**GT1b (pooled T12/PR48), n/N (%)**	**Population-based weighted average %, (95% CI)[b]**
Relapsers	119/142 (83.8)	123/140 (87.9)	GT1: 65 (60 to 70)
Partial responders	26/55 (47.3)	27/40 (67.5)	GT1a: 59 (53 to 65)
Null responders	24/88 (27.3)	22/59 (37.3)	GT1b: 71 (64 to 77)
	Non-inferiority Margin		
SAPPHIRE I (M11-646)	70%		
PEARL III (M13-961)	73%		
PEARL IV (M14-002)	65%		
SAPPHIRE II (M13-098)	60%		
PEARL II (M13-389)	64%		
TURQUOISE II (M13-099)	43%		

CI = confidence interval; GT = genotype; PR = pegylated interferon and ribavirin; PR48 = PR given for up to 48 weeks; SVR = sustained virologic response; T12 = telaprevir given for 12 weeks.

[a] Data from Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] and PEARL II (M13-389).[5]

[b] According to the manufacturer's analysis.

All trials except TURQUOISE II reported a predefined subgroup analysis based on Metavir scores (F0–F1, F2, and ≥ F3). SAPPHIRE I, SAPPHIRE II, and TURQUOISE II had a defined subgroup analysis based on HCV genotype (1a and 1b). Subgroup analysis based on response to previous treatment was defined in SAPPHIRE II, PEARL II, and TURQUOISE II.

HCV RNA values were selected for the analyses of all SVR end points based on defined visit windows. When no HCV RNA value in a visit window based on defined visit windows was available, the closest values before and after the window, regardless of the value chosen for the subsequent and preceding windows, were used for the following flanking imputation protocol:

- 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 succeeding value, the HCV RNA level was considered undetectable or unquantifiable, respectively, at this visit for this patient.
- If a patient had an unquantifiable HCV RNA level at the preceding value and an undetectable HCV RNA level at the succeeding value, or vice versa, the HCV RNA level was imputed as unquantifiable at this visit for this patient.
- If an HCV RNA value was missing within the SVR windows, then a flanking imputation approach, including backward imputation, was used. The flanking imputation approach was used first.
- If the SVR window was still missing an HCV RNA value, then a backward imputation approach was carried out in which, if the nearest HCV RNA value after the SVR window was unquantifiable or undetectable, it was used to impute the HCV RNA value in the SVR window.

The statistical plans of the included trials conducted sensitivity analyses based on the different imputation methods reported above.

HRQoL results were compared between treatment groups within each trial, and differences between groups were tested using Fisher's exact test.

a) Analysis Populations

In all trials, the intention-to-treat (ITT) and safety analysis sets included all patients who received at least one dose of the blinded study drug. Efficacy analyses were performed on the ITT population, whereas safety and baseline characteristics were performed on the safety population according to actual treatment received during most of the treatment period, even if different from the randomized treatment assignment. None of the included trials defined per-protocol datasets or analysis.

3.3 Patient Disposition

Table 8 summarizes patient disposition in the included trials. In general, the percentage of patients who discontinued their double-blind treatment was less than 2%, except in the control group of PEARL IV, which had a treatment discontinuation rate of 5.4%. Treatment discontinuation rates were higher in the open-label phases of trials (ranging from 2% to 9.8%); the highest rate of discontinuation was reported in the 24-week treatment group of TURQUOISE II. The main reason for the discontinuations was adverse events, which were highest in the 24-week group in the TURQUOISE II trial.

TABLE 8: PATIENT DISPOSITION

	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks	PBO 12 Weeks	OBV/PTV/ RTV&DSV + RBV 12 Weeks	OBV/PTV/ RTV&DSV + PBO 12 Weeks	OBV/PTV/ RTV&DSV + RBV 12 Weeks	OBV/PTV/ RTV&DSV + PBO 12 Weeks	OBV/PTV/ RTV&DSV + RBV 12 Weeks	PBO 12 Weeks	OBV/PTV/R TV&DSV + RBV 12 Weeks	OBV/PTV/ RTV&DSV 12 Weeks	OBV/PTV/ RTV&DSV + RBV 12 Weeks	OBV/PTV/ RTV&DSV + RBV 24 Weeks
Screened, N	NR		NR		436		562		324		671	
Randomized, N (%)	477	159	210	209	100	205	297	98	92	95	209	172
DB												
Treated in DB phase	473	158	210	209	100	205	297	98				
Discontinued study drug, N (%)	9 (1.9)[a]	1 (0.6)[a]	1 (0.5)	1 (0.5)	0	11 (5.4)	5 (1.7)	1 (1.0)				
AE	3(0.6)	1 (0.6)	0	0	0	2 (1.0)	3 (1.0)	0				
Non-compliant	2 (0.4)	0	0	0	0	0	0	0				
Virologic failure	0	0	0	0	0	6 (2.9)	0	0				
Withdrew consent	3 (0.6)	0	1 (0.5)	1 (0.5)	0	0	1 (0.3)	1 (1.0)				
Lost to follow-up	0	0	0	0	0	3 (1.5)	0	0				
Other	1 (0.2)	0	0	0	0	2 (1.0)	1 (0.3)	0				
OL												
Entered OL phase, N (%)	157						96		91	95	209	172
Discontinued study drug, N (%)	7 (4.5)						2 (2.1)		4 (4.4)	0	8 (4.0)	17 (9.8)
AE	3 (1.9)						1 (1.0)		2 (2.2)	0	4 (1.9)	9 (5.2)
Non-compliant	1 (0.6)						1 (1.0)		2 (2.2)	0	4 (1.9)	4 (2.3)
Virologic failure	2 (1.3)						0		0	0	0	1(0.6)
Withdrew consent	3 (1.9)						0		0	0	0	3 (1.7)
Other	0						0		0	0	0	0
Discontinued study, N (%)	9 (1.9)	6 (3.8)	0	1 (0.5)	0	7 (3.4)	6 (2.0)	1 (1.0)	1 (1.1)	0	5 (2.4)	5 (2.9)
AE	2 (0.4)	0	0	0	0	0	1 (0.3)	0	1 (1.1)	0	2 (1.0)	0
Withdrew consent	3 (0.6)	4 (2.5)	0	0	0	0	4 (1.3)	1 (1.0)	0	0	0	1 (0.6)
Entered an extension study	0	2 (1.3)	0	0	0	1 (0.5)	1 (0.3)	0	0	0	0	0
Lost to follow-up	4 (0.8)	0	0	1 (0.5)	0	3 (1.5)	0	0	0	0	0	2 (1.2)

	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks	PBO 12 Weeks	OBV/PTV/ RTV&DSV + RBV 12 Weeks	OBV/PTV/ RTV&DSV + PBO 12 Weeks	OBV/PTV/ RTV&DSV + RBV 12 Weeks	OBV/PTV/ RTV&DSV + PBO 12 Weeks	OBV/PTV/ RTV&DSV + RBV 12 Weeks	PBO 12 Weeks	OBV/PTV/R TV&DSV + RBV 12 Weeks	OBV/PTV/ RTV&DSV 12 Weeks	OBV/PTV/ RTV&DSV + RBV 12 Weeks	OBV/PTV/ RTV&DSV + RBV 24 Weeks
Other	0	1 (0.6)	0	0	0	3 (1.5)	0	0	0	0	3 (1.4)	2 (1.2)
ITT, N	473	158	210	209	100	205	297	97	88	91	208	172
PP, N	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Safety, N	473	158	210	209	100	205	297	97	91	95	208	172

AEs = adverse events; DB = double-blind; ITT = intention-to-treat; NR = not reported; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); OL = open-label; PBO = placebo; PP = per-protocol; RBV = ribavirin.

[a] Safety population.

Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

3.4 Exposure to Study Treatments

Exposure to study treatments is summarized in Table 9. In all included trials, the mean treatment duration ranged from 11.7 weeks to 12 weeks in all treatment groups. The one exception was the 24-week treatment group in TURQUOISE II, which had a mean treatment duration of 23.6 weeks.

3.5 Critical Appraisal

3.5.1 Internal Validity

Randomization and allocation concealment were well reported and shown to be effective based on equitable distribution of baseline characteristics between different treatment groups within each trial. Patients' genders were the only exception, showing different percentages of male and female distribution in all trials except TURQUOISE II. These differences could not be explained, and they were not adjusted for in the analyses. Four included studies were patient- and investigator-blinded (SAPPHIRE I, PEARL III, PEARL IV, and SAPPHIRE II); however, blinding may not have been maintained due to the known adverse events associated with RBV, such as fatigue and anemia. Furthermore, PEARL II and TURQUOISE II were open-label trials. Awareness of treatment allocation, either purposeful in the open-labelled studies or due to unblinding, might have influenced subjective measures such as HRQoL and adverse events.

All trials except TURQUOISE II shared the same limitations related to comparisons with a historical control rather than a direct comparison between trial groups, which limits the ability to assess differences between the randomized treatments. As historical controls were used as the main comparison, the primary outcome (SVR12 rate) cannot be ascertained directly from the trial. This comparative approach raises several concerns, because it compares two cohorts of interventions — i.e., it is essentially an observational study — without a mechanism to ensure that confounders are evenly distributed between groups. Thus, there is a higher chance of the observed differences being due to factors other than the evaluated treatments. Also, these trials and the trials from which the historical control rates were derived did not take place during the same time period. This opens the possibility that changes in clinical practice (for example, greater familiarity with the DAAs) may bias the observed treatment differences. In the case of historical control, no guarantee can be made that the patient populations were truly similar aside from receipt of the treatment intervention. The included trials did not adjust for confounders such as fibrosis distribution. Another limitation with this approach was that it used non-inferiority and was tested with an arbitrary reduction in the historical rate of 10.5% for the anticipated improvement of OBV/PTV/RTV and DSV in safety and convenience over existing regimens. Finally, only ITT analysis was used in the efficacy analyses, including the non-inferiority analyses. In comparison with per-protocol analyses, ITT analyses tend to show bias toward achieving non-inferiority; however, the rate of discontinuation was very small, and therefore the two populations analyses would not be expected to differ greatly.

Despite the limitations associated with historical comparisons, the trial design for these new drug regimens has been accepted by the FDA for the treatment of CHC infection.[29] However, the draft guidance document produced by the FDA noted that future treatments should use alternate study designs with an active control, once peg-IFN–free regimens are available.

3.5.2 External Validity

The included studies presented a CHC population with minimal comorbidities. Generalizability of trial results may be limited for more complex patients, as common comorbidities, including HIV co-infection, were listed as exclusion criteria in all six trials. A relatively large percentage of patients are co-infected with HCV and HIV, and there is evidence that HIV co-infection can accelerate the progression of CHC to

important complications such as cirrhosis and end-stage liver disease. One phase 2 trial was identified in the literature that evaluated OBV/PTV/RTV and DSV in patients with HIV co-infection, and this trial is summarized in Appendix 6. Other factors that may limit the generalizability of findings from these trials include the absence of relevant direct comparators such as the combination of LDV/SOF. Furthermore, the generalizability to patients with cirrhosis is limited; as only one trial, in which all patients had compensated disease, included patients with cirrhosis.

TABLE 9: EXPOSURE TO STUDY INTERVENTION

	Treatment-Naive Patients						Treatment-Experienced				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002)		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
DB Phase												
	OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 158)	OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/RTV&DSV + PBO 12 Weeks (n = 205)	OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 91)	OBV/PTV/RTV&DSV 12 Weeks (n = 95)	OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/RTV&DSV + RBV 24 Weeks (n = 172)
Duration of treatment (days)												
Mean (SD)	83.2 (9.4)	84.0 (5.2)	84.0 (1.7)	83.9 (3.1)	84.3 (0.9)	82.7 (8.7)	83.7 (6.7)	83.5 (8.7)				
Median (min., max.)	84 (1, 93)	84 (20, 89)	84 (65, 88)	84 (41, 88)	84 (81, 88)	84 (11, 96)	84 (3, 88)	85 (5, 88)				
Duration interval (days), N (%)												
1 to 15	7 (1.5)	0	0	0	0	1 (0.5)	1 (0.3)	1 (1.0)				
16 to 30	0	1 (0.6)	0	0	0	1 (0.5)	1 (0.3)	0				
31 to 45	0	0	0	1 (0.5)	0	2 (1.0)	1 (0.3)	0				
46 to 60	0	0	0	0	0	2 (1.0)	0	1 (1.0)				
61 to 75	2 (0.4)	0	1 (0.5)	0	0	3 (1.5)	1 (0.3)	0				
> 75	464 (98.1)	157 (99.4)	209 (99.5)	208 (99.5)	100 (100)	196 (95.6)	293 (98.7)	95 (97.9)				
OL Phase												
	OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 157)						OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 96)		OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 91)	OBV/PTV/RTV&DSV 12 Weeks (n = 95)	OBV/PTV/RTV&DSV + RBV 12 Weeks (n=209)	OBV/PTV/RTV&DSV + RBV 24 Weeks (n=172)
Duration of treatment (days)												
Mean (SD)	82 (10.2)						82.6 (10.0)		82.9 (9.0)	84.4 (0.8)	83.2 (9.4)	164.5 (20)
Median (min., max.)	84 (1, 96)						84 (12, 88)		84 (13, 88)	84 (83, 88)	84 (9, 88)	168 (12, 171)
Duration interval (days), N (%)												
1 to 15	2 (1.3)						1 (1.0)		1 (1.1)	0	2 (1.0)	1 (0.6)
16 to 30	0						1 (1.0)		0	0	1 (0.5)	0
31 to 45	1 (0.6)						0		1 (1.1)	0	1 (0.5)	0
46 to 60	1 (0.6)						0		0	0	0	1 (0.6)
61 to 75	2 (1.3)						0		0	0	0	1 (0.6)
> 75	151 (96.2)						94 (97.9)		89 (97.8)	95 (100)	204 (98.1)	169 (98.3)

DB = double-blind; max. = maximum; min. = minimum; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); OL = open-label; PBO = placebo; RBV = ribavirin; SD = standard deviation.

Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See Appendix 5 for detailed efficacy data.

3.6.1 Sustained Virologic Response for 12 Weeks and Relapse Rates

Table 10 summarizes the results for SVR12 and the relapse rates.

a) Sustained Virologic Response for 12 Weeks

The proportion of patients achieving SVR12 ranged from 86% to 100% in all treatment groups. The response rates — 96.2% in SAPPHIRE I, 99.5% and 99.0% in PEARL III, 97% and 90.2% in PEARL IV, 96.3% in SAPPHIRE II, 96.6% and 100% in PEARL II — were statistically superior to the historical comparator. OBV/PTV/RTV and DSV plus RBV was compared with OBV/PTV/RTV and DSV in three trials; PEARL II and PEARL III showed that the differences between the two interventions were not statistically significant (96.6% versus 100%, and 99.5 versus 99.0% for the two trials, respectively), while PEARL IV showed that OBV/PTV/RTV and DSV plus RBV was associated with a statistically significantly higher proportion of patients achieving SVR12 (97%), versus 90.2% without RBV (absolute risk difference: 6.8% [95% CI, 1.5% to 12.0%]). In TURQUOISE II, treating cirrhotic patients with 24 weeks of OBV/PTV/RTV and DSV was associated with a numerically higher proportion of patients achieving SVR12 than in the 12-week treatment group (95.9% versus 91.8%), but the difference was not statistically significant.

These findings were consistent in key subgroup analyses (by genotype and cirrhosis). SVR12 rates remained high (> 86%) regardless of genotype (1a or 1b) or the presence of cirrhosis (Appendix 5). Of note: treating cirrhotic patients, in TURQUOISE II, with OBV/PTV/RTV and DSV for 24 weeks was associated with a higher SVR12 rate than in the 12-week treatment in patients with cirrhosis who had not responded to their previous therapy (95.2% versus 86.7%), as well as in patients infected with HCV genotype 1a (94.2% versus 84.2%). SVR12 results were consistent for the three fibrosis subgroups: for the F0-F1 subgroup, the results ranged from 92.5% to 100%; for the F2 subgroup, the results ranged from 82.9% to 100%; and for the ≥ F3 subgroup, the results ranged from 90% to 100%.

b) Relapse Rate

A total of 38 cases of relapse were reported in the included trials, and there was no obvious trend to their occurrence. SAPPHIRE I and SAPPHIRE II reported seven cases each in the OBV/PTV/RTV and DSV plus RBV groups (1.5% and 2.4%, respectively). PEARL IV showed that the addition of RBV to OBV/PTV/RTV and DSV was associated with a numerically lower relapse rate (1.0%) compared with OBV/PTV/RTV and DSV alone (5.2%). In TURQUOISE II, cirrhotic patients treated for 24 weeks had a numerically lower relapse rate than their counterparts who were treated for 12 weeks only (0.6% versus 5.9%, respectively). No data on the role of resistance in relapse rates were provided.

3.6.2 Health-Related Quality of Life

Table 10 also summarizes the results for HRQoL measures.

a) SF-36 Physical Component Summary

The mean change from baseline for OBV/PTV/RTV and DSV plus RBV ranged from –0.5 points to –2.8 points. The differences in mean changes from baseline were not statistically or clinically significant between treatment groups in any of the included trials.

b) SF-36 Mental Component Summary

The mean change from baseline for OBV/PTV/RTV and DSV plus RBV ranged from –1.4 points to –3.7 points, with negative changes indicating worsening. These changes were statistically significantly lower than changes observed for placebo groups in SAPPHIRE II (–3.7 versus –0.6; *P* = 0.012). However, the differences between treatment groups in mean changes from baseline were not statistically significant in SAPPHIRE I, PEARL II, PEARL III, PEARL IV, or TURQUOISE II.

c) EuroQol 5-Dimensions Health Index Score

The EQ-5D health index uses a completely different scale, and 0.03 is considered clinically important. The EQ-5D health index scores showed mean changes from baseline ranging from –0.02 to 0.01 across treatment groups. The differences between treatment groups in mean changes from baseline were not statistically or clinically important in any of the included trials.

d) EuroQol 5-Dimensions Visual Analogue Scale

The mean changes from baseline for OBV/PTV/RTV and DSV plus RBV ranged from –1.6 points to 2.3 points. The mean changes from baseline for OBV/PTV/RTV and DSV plus RBV were statistically significantly lower than the mean changes reported for OBV/PTV/RTV and DSV alone in PEARL II (–0.2 versus 3.4; *P* = 0.044). However, none of the other trials showed a statistically or clinically significant difference between treatment groups.

e) Hepatitis C Virus Patient-Reported Outcome Instrument

HCV-PRO scores showed mean changes from baseline ranging from –4.8 points to 1.9 points. The mean changes from baseline were statistically significantly lower in the OBV/PTV/RTV and DSV plus RBV groups than in the placebo groups in SAPPHIRE I (–4.8 versus –0.6; *P* = 0.012) and SAPPHIRE II (–4.4 versus –0.9; *P* = 0.028), and they were lower than the OBV/PTV/RTV and DSV alone group in PEARL IV (–3.3 versus 1.9; *P* = 0.020). The differences in mean changes from baseline were not statistically significant in PEARL II, PEARL III, or TURQUOISE II.

3.6.3 Mortality

Two deaths were reported in the included trials, both in the OBV/PTV/RTV and DSV plus RBV groups: one case in SAPPHIRE I and one in TURQUOISE II.

TABLE 10: SUMMARY OF EFFICACY DATA

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I		PEARL III		PEARL IV		SAPPHIRE II		PEARL II		TURQUOISE II	
	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/ PTV/RTV and DSV + R BV 12 Weeks (n = 210)	OBV/ PTV/RTV and DSV + PBO 12 Weeks (n = 209)	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 100)	OBV/ PTV/RTV and DSV + P BO 12 Weeks (n = 205)	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 88)	OBV/ PTV/RTV and DSV 12 Weeks (n = 91)	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 208)	OBV/ PTV/RTV and DSV + RBV 24 Weeks (n = 172)
SVR12 (ITT population)												
N (%) [95% CI]	455 (96.2) [94.5 to 97.9]	NR	209 (99.5) [98.6 to 100]	207 (99.0) [97.7 to 100]	97 (97.0) [93.7 to 100]	185 (90.2) [86.2 to 94.3]	286 (96.3) [94.1 to 98.4]	NR	85 (96.6) [92.8 to 100]	91 (100) [95.9 to 100]	191 (91.8) [87.6 to 96.1]	165 (95.9) [92.6 to 99.3]
Difference (95% CI)	NR		–0.5 (–2.1 to 1.1)		–6.8 (–12.0 to –1.5)		NR		3.4 (–0.4 to 7.2)		–4.18 (–9.79 to 1.42)	
NI achieved	Yes	NA	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	NA	
Superiority achieved	Yes		Yes	Yes	Yes	Yes	Yes		Yes	Yes		
Relapse at week 12 post-treatment, N (%)												
n/N (%)	7 (1.5)	NR	0	0	1 (1.0)	10 (5.2)	7 (2.4)	NR	0	0	12 (5.9)	1 (0.6)
SF-36 PCS, mean (SD) change from baseline												
Baseline	52.0	49.3	52.3	52.5	50.9	49.9	50.8	50.8	52.0	51.1	48.1	47.6
Final	–1.3 (7.9)	0.7 (7.0)	–0.5 (6.8)	–0.1 (6.7)	–0.6 (7.2)	0.9	–2.8 (7.7)	–1.3 (6.3)	–2.1 (6.1)	–0.5 (5.9)	–1.1 (6.76)	–1.5 (6.8)
Difference (SE)	–0.93 (0.64); *P* = 0.147		–0.56 (0.59); *P* = 0.346		–1.32 (0.82); *P* = 0.109		–1.53 (0.80); *P* = 0.058		1.32 (0.85); *P* = 0.121		–0.56 (0.67); *P* = 0.401	
SF-36 MCS, mean (SD) change from baseline												
Baseline	49.8	49.9	50.9	50.8	51.8	48.3	50.1	48.5	47.0	49.6	48.6	47.1
Final	–3.7 (10.5)	–2.0 (9.9)	–1.4 (9.2)	–0.1 (9.1)	–2.9 (10.6)	0.3 (10.1)	–3.7 (9.7)	–0.6 (9.0)	–2.4 (8.4)	0.1 (8.5)	–2.3 (9.4)	–2.9 (10.5)
Difference (SE)	–1.73 (0.92); *P* = 0.062		–1.17 (0.81); *P* = 0.150		–2.3 (1.22); *P* = 0.060		–2.71 (1.07); *P* = 0.012		–2.81 (1.21); *P* = 0.022		–1.03 (0.99); *P* = 0.296	
EQ-5D health index score												
Baseline	0.88	0.85	0.89	0.89	0.88	0.85	0.87	0.86	0.88	0.86	0.84	0.81
Final	–0.02 (0.1)	–0.01 (0.1)	0.0 (0.12)	0.01 (0.1)	–0.04 (0.1)	–0.00 (0.1)	–0.04 (0.2)	–0.02 (0.2)	–0.02 (0.1)	0.00 (0.1)	–0.03 (0.1)	–0.02 (0.1)
Difference (SE)	–0.001 (0.011); *P* = 0.961		–0.002 (0.012); *P* = 0.836		–0.028 (0.014); *P* = 0.052		–0.025 (0.016); *P* = 0.114		0.014 (0.015); *P* = 0.372		0.01 (0.014); *P* = 0.701	
EQ VAS score, mean (SD)												
Baseline	81.2	78.9	82.5	83.7	82.6	80.3	79.0	78.6	79.3	79.1	76.1	73.0
Final	–0.6 (15.2)	–0.3 (14.1)	2.3 (13.4)	1.4 (13.3)	–0.0 (13.2)	3.5 (13.3)	–1.6 (15.1)	–1.1 (13.6)	–0.2 (12.3)	3.4 (12.1)	0.8 (15.8)	0.6 (16.8)
Difference (SE)	0.60 (1.3); *P* = 0.633		0.25 (1.14); *P* = 0.825		–2.73 (1.49); *P* = 0.068		–0.37 (1.6); *P* = 0.820		3.48 (1.72); *P* = 0.044		–1.47 (1.504); *P* = 0.330	

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I		PEARL III		PEARL IV		SAPPHIRE II		PEARL II		TURQUOISE II	
	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/ PTV/RTV and DSV + R BV 12 Weeks (n = 210)	OBV/ PTV/RTV and DSV + PBO 12 Weeks (n = 209)	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 100)	OBV/ PTV/RTV and DSV + P BO 12 Weeks (n = 205)	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 88)	OBV/ PTV/RTV and DSV 12 Weeks (n = 91)	OBV/ PTV/RTV and DSV + RBV 12 Weeks (n = 208)	OBV/ PTV/RTV and DSV + RBV 24 Weeks (n = 172)
HCV-PRO score, mean (SD)												
Baseline	79.5	77.3	81.1	82.9	80.8	76.5	77.4	78.1	77.2	77.3	74.4	70.5
Final	–4.8 (17.0)	–0.6 (14.5)	0.4 (16.7)	0.3 (15.0)	–3.3 (15.3)	1.9 (15.6)	–4.4 (16.5)	–0.9 (11.6)	–1.6 (14.6)	1.5 (13.4)	–1.8(14.9)	–2.0 (16.2)
Difference (SE)	–3.61 (1.44); *P* = 0.012		–0.51 (1.43); *P* = 0.723		–4.31 (1.84); *P* = 0.020		–3.85 (1.74); *P* = 0.028		3.19 (2.04); *P* = 0.120		–1.1 (1.6); *P* = 0.466	
Deaths												
	1	0	0	0	0	0	0	0	0	0	1	0

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; EQ VAS = EuroQol visual analogue scale; HCV-PRO = Hepatitis C Virus Patient-Reported Outcomes Instrument; ITT = intention-to-treat; MCS = mental component summary; NI = non-inferiority; NR = not reported; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; PCS = physical component summary; SD = standard deviation; SE = standard error; SF-36 = Short-Form 36-Item Health Survey; SVR12 = sustained virologic response for 12 consecutive weeks.
Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). Table 11 summarizes the adverse events data.

3.7.1 Adverse Events

Rates of adverse events were high across all treatment groups in the included trials, ranging from 67% to 92%. OBV/PTV/RTV and DSV plus RBV were associated with higher rates of adverse events than the placebo groups in SAPPHIRE I (87.5% versus 73.4%) and SAPPHIRE II (91.2% versus 82.5%). It was also associated with a higher rate of adverse events than OBV/PTV/RTV and DSV alone in PEARL III (80.0% versus 67.0%) and in PEARL IV (92.0% versus 82.4%); however, PEARL II showed similar rates for the two groups in PEARL II (79.1% versus 77.9%).

3.7.2 Withdrawal Due to Adverse Events

Adverse events leading to drug discontinuation were relatively rare (≤ 2.3%) in all treatment groups.

3.7.3 Serious Adverse Events

The rates of serious adverse events (SAEs) ranged from 0% to 6.3% across treatment groups in the included studies. Cirrhotic patients in TURQUOISE II reported the highest rate of SAEs (6.3% versus 4.7% for the 12- and 24-week treatment groups, respectively).

3.7.4 Notable Harms

Patients treated with OBV/PTV/RTV and DSV plus RBV reported the occurrence of fatigue (32% to 46%), nausea (11% to 24%), insomnia (9% to 15%), rash (5% to 11%), pruritus (14% to 18%), depression (2% to 4%), photosensitivity (0% to 1%), anemia (5% to 11%), and neutropenia (0% to 1%).

Compared with placebo, the combination OBV/PTV/RTV and DSV plus RBV was associated with higher rates of fatigue (5% to 10%), nausea (5% to 14%), insomnia (7%), rash (2% to 4%), pruritus (8% to 13%), and anemia (5%). However, it was associated with similar rates of depression, photosensitivity, and neutropenia.

Comparing OBV/PTV/RTV and DSV plus RBV versus OBV/PTV/RTV and DSV without RBV showed that the addition of RBV was associated with higher rates of fatigue (11% to 15%), nausea (5% to 14%), insomnia (6% to 11%), rash (0% to 7%), pruritus (4% to 6%), and anemia (6% to 11%). The addition of RBV didn't affect the occurrence of depression, photosensitivity, or neutropenia.

TABLE 11: SUMMARY OF ADVERSE EVENTS

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I		PEARL III		PEARL IV		SAPPHIRE II		PEARL II		TURQUOISE II	
	OBV/ PTV/ RTV&DSV + RBV (n = 473)	PBO (n = 157)	OBV/PTV / RTV&DSV + RBV (n = 210)	OBV/PTV / RTV&DSV + PBO (n = 209)	OBV/PTV / RTV&DSV + RBV (n = 100)	OBV/PTV / RTV&DSV + PBO (n = 205)	OBV/PTV / RTV&DSV + RBV (n = 297)	PBO (n = 97)	OBV/PTV / RTV&DSV + RBV (n = 88)	OBV/PTV / RTV&DSV (n = 91)	OBV/PTV/ RTV&DSV + RBV (n = 208)	OBV/PTV/ RTV&DSV + RBV (n = 172)
AEs	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	24 weeks
Any AE	414 (87.5)	116 (73.4)	168 (80.0)	140 (67.0)	92 (92.0)	169 (82.4)	271 (91.2)	80 (82.5)	72 (79.1)	74 (77.9)	191 (91.8)	156 (90.7)
SAE	10 (2.1)	0	4 (1.9)	4 (1.9)	3 (3.0)	1 (0.5)	6 (2.0)	1 (1.0)	2 (2.2)	2 (2.1)	13 (6.3)	8 (4.7)
AE leading to discontinuation of study drug	3 (0.6)	1 (0.6)	0	0	0	2 (1.0)	3 (1.0)	0	2 (2.2)	0	4 (1.9)	4 (2.3)
Common AE												
Fatigue	164 (34.7)	45 (28.5)	45 (21.4)	48 (23.0)	46 (46.0)	72 (35.1)	99 (33.3)	22 (22.7)	29 (31.9)	15 (15.8)	68 (32.7)	80 (46.5)
Headache	156 (33.0)	42 (26.6)	51 (24.3)	49 (23.0)	25 (25.0)	58 (28.3)	108 (36.4)	34 (35.1)	22 (24.2)	22 (23.2)	58 (27.9)	53 (30.8)
Insomnia	66 (14.0)	12 (7.6)	19 (9.0)	7 (3.3)	17 (17.0)	16 (7.8)	42 (14.1)	7 (7.2)	13 (14.3)	3 (3.2)	32 (15.4)	31 (18.0)
Nausea	112 (23.7)	21 (13.3)	23 (11.0)	9 (4.3)	21 (21.0)	28 (13.7)	60 (20.2)	17 (17.5)	19 (20.9)	6 (6.3)	37 (17.8)	35 (20.3)
Asthenia	57 (12.1)	6 (3.8)	22 (10.5)	11 (5.3)	3 (3.0)	2 (1.0)	47 (15.8)	11 (11.3)	11 (12.1)	7 (7.4)	29 (13.9)	22 (12.8)
Diarrhea	65 (13.7)	11 (7.0)	9 (4.3)	13 (6.2)	14 (14.0)	33 (16.1)	39 (13.1)	12 (12.4)	12 (13.2)	12 (12.6)	30 (14.4)	29 (16.9)
Rash	51 (10.8)	9 (5.7)	12 (5.7)	8 (3.8)	5 (5.0)	10 (4.9)	26 (8.8)	6 (6.2)	8 (8.8)	1 (1.1)	23 (11.1)	25 (14.5)
Irritability	25 (5.3)	4 (2.5)	0	1 (0.5)			16 (5.4)	8 (8.2)	5 (5.5)	1 (1.1)	15 (7.2)	21 (12.2)
Cough	35 (7.4)	8 (5.1)	19 (9.0)	5 (2.4)	5 (5.0)	12 (5.9)	32 (10.8)	5 (5.2)	3 (3.3)	7 (7.4)	24 (11.5)	19 (11.0)
Dyspnea	38 (8.0)	4 (2.5)	7 (3.3)	3 (1.4)	4 (4.0)	6 (2.9)	37 (12.5)	9 (9.3)	8 (8.8)	2 (2.1)	12 (5.8)	21 (12.2)
Pruritus	80 (16.9)	6 (3.8)	25 (11.9)	11 (5.3)	10 (10.0)	12 (5.9)	41 (13.8)	5 (5.2)	13 (14.3)	8 (8.4)	38 (18.3)	33 (19.2)
Depression	21 (4.4)	3 (1.9	4 (1.9)	5 (2.4)	1 (1.0)	4 (2.0)	7 (2.4)	3 (3.1)			8 (3.8)	12 (7.0)
Photosensitivity	1 (0.2)	1 (0.2)	0	2 (1.0)	0	3 (1.5)	2 (0.7)	1 (1.0)			1 (0.5)	2 (1.2)
Hypertension	9 (1.9)	0	5 (2.4)	2 (1.0)	0	2 (1.0)	8 (2.7)	2 (2.1)	5 (5.5)	4 (4.2)		

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I		PEARL III		PEARL IV		SAPPHIRE II		PEARL II		TURQUOISE II	
	OBV/ PTV/ RTV&DSV + RBV (n = 473)	PBO (n = 157)	OBV/PTV / RTV&DSV + RBV (n = 210)	OBV/PTV / RTV&DSV + PBO (n = 209)	OBV/PTV / RTV&DSV + RBV (n = 100)	OBV/PTV / RTV&DSV + PBO (n = 205)	OBV/PTV / RTV&DSV + RBV (n = 297)	PBO (n = 97)	OBV/PTV / RTV&DSV + RBV (n = 88)	OBV/PTV / RTV&DSV (n = 91)	OBV/PTV/ RTV&DSV + RBV (n = 208)	OBV/PTV/ RTV&DSV + RBV (n = 172)
Palpitation	11 (2.3)	3 (1.0)	4 (1.9)	1 (0.5)	1 (1.0)	1 (0.5)	6 (2.0)	1 (1.0)	5 (5.5)	2 (2.1)		
Anemia	25 (5.3)	0	14 (6.7)	1 (0.5)	6 (6.0)	0	16 (5.4)	0	10 (11.0)	0	16 (7.7)	18 (10.5)
Hematologic AE, n/N (%)												
Lymphocyte count (< 0.5 × 10^9/L)	1 (0.2)	0	0	0	1 (1.0)	0	0	0	0	0	5/207 (2.4)	3/172 (1.7)
Neutrophil count (< 1 × 10^9/L)	1 (0.2)	0	1 (0.5)	0	0	0	0	2 (2.1)	0	0	1/207 (0.5)	3/172 (1.7)
Platelet count (< 50 × 10^9/L)	0	0	0	1 (0.5)	0	0	0	0	0	0	2/207 (1.0)	0
Hemoglobin (< 80 g/L)	0	0	1 (0.5)	0	1 (1.0)	0	1 (0.3)	0	0	0	3 (1.5)	1 (0.6)

AEs = adverse events; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; RBV = ribavirin; SAE = serious adverse event.

Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

4. DISCUSSION

4.1 Summary of Available Evidence

Six trials met the inclusion criteria for this systematic review. Four trials were DB, and two trials had an open-label design. The trials included patients infected with CHC virus genotype 1; three trials included patients with no previous experience with antiviral treatment for hepatitis C infection, two trials included patients who had failed previous antiviral treatment, and one trial included both treatment-naive and treatment-experienced patients who had cirrhosis. The trials evaluated 12-week treatment with OBV/PTV/RTV and DSV plus RBV relative to placebo (two trials), OBV/PTV/RTV and DSV alone (three trials), or OBV/PTV/RTV and DSV plus RBV administered for 24 weeks (one trial).

The main outcome in the included trials was the proportion of patients achieving SVR12. The main limitation of the included trials was the lack of an active treatment comparator group consisting of an existing treatment regimen for CHC genotype 1 infection. The primary outcome was compared with a historical control (SVR12 rates from trials that evaluated TEL + PR). Comparison to a historical control could be biased due to differences in the distribution of potential confounders of effect. Currently recommended interferon-free comparators include LDV/SOF and SOF/SIM.[30]

4.2 Interpretation of Results

4.2.1 Efficacy

The manufacturer is seeking listing for OBV/PTV/RTV and DSV for the treatment of genotype 1 CHC infection, including for patients who are treatment-naive or who have failed previous therapies against HCV, and patients with compensated cirrhosis. The listing criteria reflects the Health Canada–approved indication and the most recent Canadian guidelines.[30] In patient group input received by CDR for this submission, patients' expectations were that the drug would cure their infection and provide treatment options for those receiving liver transplants, or for those who did not respond to or could not tolerate previous therapies (due to HIV co-infection, autoimmune conditions, or other comorbidities) (see **Error! eference source not found.** for patient input summary).

In non-cirrhotic patients infected with genotype 1b, the Health Canada–approved regimen of OBV/PTV/RTV and DSV without RBV was associated with high rates of successful treatment: 100% of patients achieved SVR12 in PEARL III and PEARL II. These rates were higher (absolute difference ≥ 16%) than the historical comparator (TEL + PR). In non-cirrhotic patients infected with genotype 1a, however, the Health Canada–approved indication includes RBV in addition to OBV/PTV/RTV and DSV. In SAPPHIRE I and SAPPHIRE II, SVR12 rates with OBV/PTV/RTV and DSV and RBV were lower in genotype 1b than in the genotype 1a population (95.3% and 96.3%, respectively).

For cirrhotic patients, the response rates were lower than those reported for non-cirrhotic patients, ranging from 87% to 100% depending on previous experience with HCV antiviral therapies. For these patients, Health Canada recommends RBV in addition to OBV/PTV/RTV and DSV for 12 weeks for all patients, except those infected with genotype 1a and who had null response to their previous therapy. For these patients, the approved treatment duration is 24 weeks instead of 12 weeks.

TURQUOISE I reported similar response results for CHC patients co-infected with HIV (Appendix 6). TURQUOISE I was excluded from the current systematic review because it was a pilot phase 2 trial. Sixty-three patients were randomized into 12- and 24-week treatments with OBV/PTV/RTV and DSV and RBV. The trial reported SVR12 rates of 93.5% and 90.6% for the two groups, respectively. The generalizability of these results is limited for patients excluded from TURQUOISE I; these included patients co-infected

with HBV or HIV-2, patients with decompensated cirrhosis, or patients who experienced treatment failure with two or more antiretroviral (ART) regimens.[31] The American Association for the Study of Liver Disease (AASLD) recommends the use of OBV/PTV/RTV and DSV plus RBV for HIV patients in addition to their ART drugs, if there are no substantial interactions, such as raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine, and atazanavir.[32] According to AASLD guidelines, however, OBV/PTV/RTV and DSV should not be used for HIV patients who are not taking ART therapy, and for patients treated with efavirenz, rilpivirine, darunavir, or ritonavir-boosted lopinavir.[32]

The included trials reported few cases of relapse (38 cases) and death (two cases). The reported relapses could not be associated with specific treatment regimens or patient characteristics, and because of the low incidence, the trials did not report any statistical testing for this outcome. The two deaths were both in the OBV/PTV/RTV and DSV plus RBV groups.

Patient group input emphasized the impact that CHC has on patients' quality of life. The trials of OBV/PTV/RTV and DSV evaluated HRQoL using two generic instruments — namely the SF-36 and EQ-5D — and one HCV-specific instrument, the HCV-PRO). HCV-PRO appears to be a validated instrument that demonstrated convergent validity with other instruments, such as the SF-36 physical component summary (PCS) and mental component summary (MCS) scores and the EuroQol visual analogue scale (EQ VAS). Overall, there were no statistically significant differences between the treatment groups within each trial, and HRQoL did not deteriorate significantly through treatment, unlike what is typically seen with HRQoL scores from other DAA regimens that include PR.[33] However, in the absence of HRQoL data comparing OBV/PTV/RTV and DSV with other regimens, the extent to which OBV/PTV/RTV and DSV 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 these pivotal trials, most notably LDV/SOF. Phase 3 trials for LDV/SOF also used historical controls as their primary comparator, and achieved high (> 90%) response rates in treatment-naive, treatment-experienced, cirrhotic, and non-cirrhotic study participants.[19] While small differences in absolute SVR12 rates may exist between LDV/SOF and OBV/PTV/RTV and DSV based on the results of these trials, it is difficult to reliably compare the efficacy of these two regimens without a direct or indirect comparison. 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-group data, methodologies for using these data are available, and previous submissions for CHC treatments included indirect comparisons that incorporated single-group data.[19]

4.2.2 Harms

Patient group input described adverse events associated with current peg-IFN–based therapies as severe and debilitating. Hence, it is expected that peg-IFN–free regimens such as OBV/PTV/RTV and DSV will be better tolerated than older regimens. Two included trials, SAPPHIRE I and SAPPHIRE II, compared OBV/PTV/RTV and DSV plus RBV with placebo. This comparison permits the evaluation of treatment-emergent adverse events. For example, insomnia, pruritus, and palpitation were reported at more than double the rate in the OBV/PTV/RTV and DSV groups than with placebo. Other adverse events, such as fatigue, headache, nausea, and rash, were also commonly reported; however, these events were more likely to be due to RBV, as seen in the three PEARL trials that compared OBV/PTV/RTV and DSV with and without RBV. The PEARL trials showed that the addition of RBV to OBV/PTV/RTV and DSV was associated with higher rates of insomnia (absolute difference of 6% to 11%), nausea (5% to 14%), pruritus (4% to 5%), and anemia (6% to 11%). It is worth noting that SAEs were relatively lower in comparison with PR-based therapies evaluated in the CADTH Therapeutic Review of CHC.[33] However,

the relative safety of OBV/PTV/RTV and DSV relative to other available HCV therapies is inconclusive without a direct or indirect comparative evaluation.

While no direct or indirect statistical comparisons are available, observed rates of adverse effects with OBV/PTV/RTV and DSV without RBV appear higher than rates reported in trials evaluating LDV/SOF.[19] These include fatigue (16% to 35% versus 21% to 22%), headache (23% to 28% versus 15% to 26%), and depression (0% to 4% versus 0% to 2%), but an association with lower frequency of insomnia (3% to 8% versus 7% to 9%) and nausea (4% to 14% versus 11%). The addition of RBV to OBV/PTV/RTV and DSV was associated with even higher rates of these adverse events, including a higher rate of anemia that was not observed with LDV/SOF.

5. Conclusions

Six pivotal trials were included in this review. OBV/PTV/RTV and DSV administered according to the Health Canada–approved regimen was associated with high rates of SVR12 in patients with genotype 1 CHC infection, in both treatment-naive and treatment-experienced patients. TheSVR12 rates were higher than those reported for the historical comparator rate derived from previous TEL and PR trials. HRQoL measures showed clinically insignificant changes from baseline, and differences between treatment groups in each trial were inconsistent between the different HRQoL measures.

SAEs and withdrawals due to adverse events were infrequent. Characteristic adverse events associated with Peg-IFN appeared to occur less frequently among patients treated with OBV/PTV/RTV and DSV. However, the relative efficacy and safety of OBV/PTV/RTV and DSV compared with more recent IFN-free HCV therapies is uncertain due to the absence of direct or indirect comparative evaluations.

APPENDIX 1: PATIENT INPUT SUMMARY

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

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

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization whose mandate is to address access to treatment, care, and support for people living with human immunodeficiency virus (HIV) or hepatitis C virus (HCV). Full membership is limited to persons living with HIV/AIDS or organizations with a substantial HIV/AIDS mandate. CTAC has received unrestricted educational grants from AbbVie and other pharmaceutical companies.

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

Hepatitis C Education and Prevention Society (HepCBC) is a non-profit organization run by and for people affected by HCV in British Columbia. HepCBC focuses on providing peer support groups, anti-stigma activities, prevention education, and general hepatitis information, and encouraging testing among at-risk groups. HepCBC received funding from pharmaceutical companies, including AbbVie, to support its educational activities, and the author of this submission received funding to attend conferences.

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

2. Condition- and Current Therapy-Related Information
The information for this section was gathered through online surveys and interviews with patients affected by HCV, caregivers, and health care professionals from across Canada.

HCV is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, cancer, liver failure, and even death. For those co-infected with HIV, liver disease progression may be exacerbated. Some patients have few or no symptoms, but others experience fatigue, general weakness, abdominal, muscle or joint pain, itchiness, poor circulation, constipation, nausea, loss of appetite, headaches, disrupted sleep, and jaundice. In some patients, the disease affects cognitive functions, and they find it difficult to function when their thinking, understanding, memory, or focus is impeded. 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,

which may lead to depression, anxiety, loss of hope, and social isolation. Often marriages and other personal relationships cannot survive the strain. To patients, a cure means freedom from debilitating fatigue and stigma-centred fear, and optimism that their risk for liver cancer, liver failure, and liver transplant will soon decrease.

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

Current therapy is up to 48 weeks in duration and may include boceprevir, telaprevir (TEL) or simeprevir (SIM). Adverse effects can be severe and debilitating, such as extreme fatigue, anemia, depression, anxiety, mood swings, rashes, headaches, chills, nausea, weight loss, suppressed appetite, hair loss, and joint pain. In addition, some triple-therapy regimens require patients to take up to 20 pills throughout the day, with specific food requirements, and have adverse drug interactions with antiretroviral (ART) therapies. Patients have no way of knowing if the treatments will be successful and if their efforts to complete therapy and endure the side effects will be worth it. Adverse effects of treatment may affect patients' ability to continue working and to manage their household or childcare. A patient who had experience with interferon-based treatment reported eyesight damage. Many patients have contraindications or cannot tolerate interferon and thus are ineligible for interferon-based regimens. Injections associated with interferon can be a triggering factor and a source of anxiety for those with a history of injection drug use. Those who have failed interferon-based treatments have few treatment options.

3. Related Information About the Drug Being Reviewed

Ombitasvir/paritaprevir/ritonavir and dasabuvir (OBV/PTV/RTV and DSV) is an all-oral treatment regimen that involves taking pills twice a day (three pills in the morning and one in the evening, for a total of four pills per day). OBV/PTV/RTV and DSV is the second therapy to offer an interferon-free option for HCV patients. For most patients, this therapy will require the addition of ribavirin (RBV), a drug known to have a high incidence of adverse events (AEs). However, the severity of these AEs usually develops over time, so patients are optimistic that the shorter treatment time will help mitigate RBV-induced AEs, as well as any AEs associated with the other ingredients. Although it requires a slightly more complex daily regimen compared with Harvoni, the length of treatment is 12 weeks, equivalent to Harvoni, and significantly shorter than older regimens. CTAC reported that the pill burden of four pills over two dosing periods per day, combined with food, can be a potential inconvenience to patients and a possible negative influence on adherence.

The foremost expectation is that the treatment's higher sustained virologic response (SVR), which have been achieved in clinical trials, will translate into a better chance of a cure for patients and, thus, enable them to start their lives anew. It is expected that OBV/PTV/RTV and DSV will open up treatment to patients receiving liver transplants, and to patients who did not respond to or could not tolerate previous therapies (due to HIV co-infection, autoimmune conditions, or other comorbidities). It is expected that OBV/PTV/RTV and DSV will have far fewer adverse side effects than current and past treatments.

OBV/PTV/RTV and DSV have high cure rates, which, along with affordability and interferon-free therapy, are the most important treatment-related factors reported by patients. With a cure, they expect that their cirrhosis will reverse, and their risk of end-stage liver disease will be reduced. Some may be able to return to work, and the quality of life of everyone will improve. Decreasing treatment duration is a priority for patients and health care providers because of its impact on adherence and the burden of side effects, and to expedite patients' return to their normal lives.

Based on feedback from individuals who have experience with OBV/PTV/RTV and DSV, the treatment was generally easy to tolerate. Patients noted that they had achieved SVR with few side effects; fatigue was reported as one of these. One patient stated that they had expected the treatment to be harder than it was. Patient advocates are very excited at the prospect of actually being able to eradicate the disease entirely from the world, although the price of the treatment will have to be greatly reduced.

APPENDIX 2: LITERATURE SEARCH STRATEGY

Electronic Databases

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:	January 21, 2015
Alerts:	Weekly search updates until May 20, 2015.
Study types:	No search filters were applied.
Limits:	No date or language limits were used. Conference abstracts were excluded.
Syntax Guide	
.sh	At the end of a phrase, searches the phrase as a subject heading.
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary.
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

Multi-database Strategy	
#	**Searches**
1	(Holkira* or Viekira*).ti,ab,ot,sh,hw,rn,nm.
2	Viekirax*.ti,ab,ot,sh,hw,rn,nm.
3	(1258226-87-7 or 1444832-14-7).rn,nm.
4	(ABT-267* or ABT267* or ombitasvir*).ti,ab,ot,sh,hw,rn,nm.
5	3 or 4
6	(ABT-450* or ABT450* or paritaprevir*).ti,ab,ot,sh,hw,rn,nm.
7	1221573-85-8.rn,nm.
8	Ritonavir/
9	(ritonavir* or Norvir* or RTV or TMC114r or TMC-114r or Abbott-84538 or A-84538 or HSDB-7160 or HSDB7160 or ABT538 or ABT-538 or DRG-0244 or DRG0244 or ABT84538 or ABT-84538).ti,ab,ot,sh,hw,rn,nm.
10	155213-67-5.rn,nm.
11	6 or 7 or 8 or 9 or 10
12	(dasabuvir* or Exviera* or ABT-333* or ABT333*).ti,ab,ot,sh,hw,rn,nm.
13	(1132935-63-7 or 1221573-79-0).rn,nm.
14	or/12-13

Multi-database Strategy	
15	and/5,11,14
16	and/2,14
17	or/1,15-16
18	17 use pmez
19	(Holkira* or Viekira*).ti,ab.
20	Viekirax*.ti,ab.
21	*ombitasvir/
22	(ABT-267* or ABT267* or ombitasvir*).ti,ab.
23	21 or 22
24	*abt 450/
25	(ABT-450* or ABT450* or paritaprevir*).ti,ab.
26	*ritonavir/
27	(ritonavir* or Norvir* or RTV or TMC114r or TMC-114r or Abbott-84538 or A-84538 or HSDB-7160 or HSDB7160 or ABT538 or ABT-538 or DRG-0244 or DRG0244 or ABT84538 or ABT-84538).ti,ab.
28	24 or 25 or 26 or 27
29	*dasabuvir/
30	(dasabuvir* or Exviera* or ABT-333* or ABT333*).ti,ab.
31	or/29-30
32	and/23,28,31
33	and/20,31
34	19 or 32 or 33
35	34 use oemezd
36	35 not conference abstract.pt.
37	18 or 36
38	remove duplicates from 37

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:	December 2014 – January 2015
Keywords:	OBV/PTV/RTV and DSV (ombitasvir, paritaprevir, ritonavir, dasabuvir)
Limits:	No date or language limits used

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

- Health technology assessment agencies
- Health economics
- Clinical practice guidelines
- Drug and device regulatory approvals
- Advisories and warnings
- Drug class reviews
- Databases (free)
- Internet search.

APPENDIX 3: LIST OF EXCLUDED STUDIES

The following three studies were excluded from the systematic review because they were phase 2 trials:

TURQUOISE I (M14-004)
Eron JJ, Lalezari J, Slim J, Gathe J, Ruane PJ, Wang C, et al. Safety and efficacy of ombitasvir - 450/r and dasabuvir and ribavirin in HCV/HIV-1 co-infected patients receiving atazanavir or raltegravir ART regimens. J Int AIDS Soc [Internet]. 2014 [cited 2015 Jan 22];17(4 Suppl 3):19500. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4224905/pdf/JIAS-17-19500.pdf

CORAL-I
Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R, Jr., et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med [Internet]. 2014 Dec 18 [cited 2015 Jan 22];371(25):2375-82. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1408921

AVIATOR
Poordad F, Agarwal K, Younes Z, Cohen D, Xie W, Podsadecki T. Low relapse rate leads to high concordance of sustained virologic response (SVR) at 12 weeks with SVR at 24 weeks after treatment with ABT-450/ritonavir, ombitasvir, and dasabuvir plus ribavirin in subjects with chronic hepatitis C virus genotype 1 infection in the AVIATOR Study. Clin Infect Dis. 2014 Nov 2.

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To review the validity of sustained virologic response at 12 weeks (SVR12) as a surrogate for sustained virologic response (SVR) at 24 weeks (SVR24) and to summarize the characteristics of the following patient-reported outcome instruments:

- Short-Form 36-Item Health Survey (SF-36)
- EuroQol 5-Dimensions Questionnaire (EQ-5D)
- Hepatitis C Virus Patient-Reported Outcomes Instrument (HCV-PRO).

Findings

Sustained Virologic Response

SVR24 is the standard primary end point for assessing response to drugs that treat CHC infection.[34] 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.[34] The authors reviewed data submitted to the FDA (2002-2011) from 15 phase 2 and 3 studies that included various treatment durations of Peg-IFN alpha-2a, Peg-IFN alpha-2b, albinterferon alpha-2b, TEL, and d boceprevir. The majority of the 13,599 participants were genotype 1 (N = 11,730), while genotype 2 (N = 783) and genotype 3 (N = 995) made up most of the remainder. In addition to assessing SVR12, the authors also reviewed the predictive value of sustained virologic response at four weeks (SVR4) with respect to SVR24.

SVR12 was achieved by 51.8% (7,051 of 13,599 patients) and SVR24 by 50.6% (6,881 of 13,599 patients) of adults in the database.[34] 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 CHC treatments.[34] They also stated that these conclusions should be applied with caution to DAA–only regimens, considering that they were based on data from regimens containing IFN plus RBV.[34] Further monitoring of IFN-free clinical trials may be required to determine the appropriate end point.

A study published in 2010 also evaluated the relevance of SVR12 as a primary outcome.[35] This study included 781 patients with CHC; all had received Peg-IFN plus RBV (PR). Of the 781 patients, 573 had an end-of-treatment response and were thus included in the analysis. Of the 409 patients who had an SVR12, 408 went on to have an SVR24.[35] 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.[31] The authors pooled single-group data for peg-IFN alpha 2a or alpha 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 and Laird random-effects model. Data for SVR12, SVR24, and for each type of peg-IFN 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 peg-IFN. The authors concluded that SVR12 was 5% to 6% higher than SVR24, although the credible intervals overlapped in the conventional meta-analysis, and in the Bayesian meta-regression the credible intervals included the null value (SVR12 versus SVR24 relative risk 1.13; 95% credible interval [CrI], 0.99 to 1.26).[31] These findings should be interpreted with caution, considering that they were based on single treatment group data. Naive pooling of single-group data is not an acceptable method to determine comparative efficacy, as it ignores the benefits of randomization and may therefore be subject to the same biases as a comparison of independent cohort studies. In addition, the analysis was limited to data from patients who received 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).[36] From this analysis, a total of 777 of 779 patients (99.7%) who achieved SVR12 also achieved SVR24, including all patients (n = 296) with CHC genotype 1 or 4 to 6, all patients (n = 270) with genotype 2, and 211 of 213 patients (99.0%) with genotype 3. Thus, the negative predictive value measuring concordance between SVR12 and SVR24 was 100% and the positive predictive value was 99.7%.

Short-Form 36-Item Health Survey

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. SF-36 consists of eight domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems. SF-36 also provides two component summaries: the physical component summary (SF-36-PCS) and the mental component summary (SF-36-MCS). SF-36-PCS, SF-36-MCS, and eight domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of SF-36, a change of 2 to 4 points in each domain or 2 to 3 points in each component summary indicates a clinically meaningful improvement, as determined by the patient.[37]

A systematic review was conducted to identify and provide information on HRQoL instruments for HCV.[38] The authors identified 32 studies and presented the results by types of clinical anchors (for example, HCV status or liver disease severity anchors), but it was not clear in the publication which instruments contributed to the data. Nonetheless, from the publication, two results attributed to SF-36 could be extracted:

- A total of 15 studies with SF-36 were included that compared HRQoL in patients with compensated HCV seropositivity versus healthy controls. All 15 studies provided cross-sectional group mean HRQoL differences stratified by HCV status (the clinical anchor). Patients with HCV scored lower on the various domains compared with healthy patients. The largest impact of the disease was on role physical, role emotional, and general health (Table 12).[38]
- A panel of experts was convened to indirectly estimate the minimal clinically important difference (MCID) in HCV based upon existing HRQoL data.[38] The panel consisted of three hepatologists and two HRQoL methodologists with expertise in chronic liver disease–specific HRQoL. Based on the results of the systematic review, the panel determined that the SF-36 vitality scale captures the HRQoL domain that is most relevant to patients with HCV. Using a modified Delphi technique, the expert panel generated a mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale, with a corresponding effect size of 0.2 (range 0.15 to 0.25).[38] MCIDs for other dimensions or for the two component scores were not estimated. Of note: this study did not use the preferred methods to

generate the MCID and it is unclear whether the estimates represent values that patients would identify as clinically important.

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

TABLE 12: PATIENT WITH HEPATITIS C VIRUSVERSUS HEALTHY CONTROL WEIGHTED MEAN AND MEDIAN CROSS-SECTIONAL DIFFERENCE (15 STUDIES)

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

EuroQol 5-Dimensions (from Cimzia AS)

The EQ-5D is a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments.[39,40] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3), representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function (EQ-5D index score) can be used to assign a value to self-reported health states from a set of population-based preference weights.[39,40] The second part is a 20 cm visual analogue scale (VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

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

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale have ranged from 0.033 to 0.074.[41]

The investigators of the included studies 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".[42] The validity of the 5L version was compared with the standard version among patients with chronic hepatic diseases (n = 1,088).[42] 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.

Hepatitis C Virus Patient-Reported Outcomes 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.[43] The HCV-PRO contains 16 items with five levels of response choices, ranging between ''all of the time'' (1) and ''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] x 100) /64.[44] 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 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 (probability value [*P*] < 0.01). In a separate study among CHC patients (n = 74),[45] 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 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 or MCS and EQ VAS MID thresholds), a MCID of –10 points was reported.[44]

Summary

- A review using individual patient data from 15 phase 2 and 3 studies (N = 13,599 participants), in which the majority were patients with genotype 1 (N = 11,730), suggests that SVR12 is a reliable surrogate for SVR24. The authors suggest that SVR12 may become a new definition for sustained virologic response for regulatory approval.
- SF-36, a generic health assessment questionnaire, has shown good construct validity in patients with HCV. A mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale has been reported. MCIDs for other dimensions or for the two component scores of the SF-36 for patients with CHC infection were not found in the literature.

- The generic EQ-5D HRQoL 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, consistent, and have a lower ceiling effect in comparison with the standard version.[42] The MCID for the EQ-5D-5L among CHC patients remains unknown.
- The HCV-PRO is a HRQoL instrument specific for patients with CHC. The HCV-PRO has demonstrated convergent validity with other instruments, such as SF-36 PCS/MCS scores and EQ VAS. The HCV-PRO has also demonstrated low ceiling/floor effects, and high internal consistency reliability. The reported MCID is –10 points.

APPENDIX 5: DETAILED OUTCOMES

TABLE 13: SUMMARY OF SUBGROUP ANALYSIS FOR SVR12

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002)		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 88)	OBV/PTV/ RTV&DSV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/ RTV&DSV +RBV 24 Weeks (n = 172)
Subgroup analysis: treatment history, n/N (%)												
Treatment-naive	473/473 (100)	157/157 (100)	210/210 (100)	209/209 (100)	100/100 (100)	205/205 (100)	NA				81/ 86 (94.2)	70/ 74 (94.6)
Treatment-experienced	NA						286/297 (96.3)	NR			110/122 (90.2)	95/98 (96.9)
Prior null responder							139/146 (95.2)		29/31 (93.5)	32/32 (100)	65/75 (86.7)	59/62 (95.2)
Prior partial responder							65/65 (100)		24/25 (96.0)	26/26 (100)	17/18 (94.4)	13/13 (100.0)
Prior relapse							82/86 (95.3)		32/32 (100)	33/33 (100)	28/29 (96.6)	23/23 (100.0)
Subgroup analysis: genotype subtype, n/N (%)												
1A	307/322 (95.3)				100/100 (100)	205/205 (100)	166/173 (96.0)				124/140 (88.6)	114/121 (94.2)
1B	148/151 (98.0)		210/210 (100)	209/209 (100)			120/124 (96.8)		88/88 (100)	91/91 (100)	67/ 68 (98.5)	51/ 51 (100.0)
Subgroup analysis: baseline fibrosis stage, n/N (%)												
F0-F1	352/363 (97.0)	NR	149/150 (99.3)	141/141 (100)	61/63 (96.8)	122/132 (92.4)	197/202 (97.5)	NR	61/63 (96.8)	59/59 (100)	Patients had compensated cirrhosis	
F2	66/70 (94.3)		38/38 (100)	47/47 (100)	20/21 (95.2)	29/35 (82.9)	50/53 (94.3)		13/13 (100)	19/19 (100)		
F3 or greater	37/40 (92.5)		22/22 (100)	18/20 (90.0)	16/16 (100)	34/38 (89.5)	39/42 (92.9)		11/12 (91.7)	13/13 (100)		

NA = not applicable; NR = not reported; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; RBV = ribavirin; SVR12 = sustained virologic response for 12 consecutive weeks.

Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

TABLE 14: SUMMARY OF SHORT-FORM 36-ITEM HEALTH SURVEY PHYSICAL COMPONENT SCALE

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002)		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV /RTV& DSV + RBV 12 Weeks (n = 88)	OBV/PTV/ RTV&DSV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/RTV &DSV + RBV 24 Weeks (n = 172)
SF-36 PCS, mean (SD) change from baseline												
On-treatment												
Baseline	52.0	49.3	52.3	52.5	50.9	49.9	50.8	50.8	52.0	51.1	48.1	47.6
Week 4	–1.4 (7.1)	–0.0 (7.4)	–1.1 (5.7)	–0.5 (5.5)	–0.9 (7.9)	0.1 (6.1)	–2.2 (6. 7)	–1.2 (4.6)	–2.0 (5.0)	–0.2 (5.5)	–1.3(6.4)	–1.5 (7.5)
Week 8	–1.9 (7.4)	0.2 (7.1)	–0.8 (6.8)	–0.2 (6.4)	–1.0 (7.3)	0.4 (7.3)	–3.0 (7.5)	–0.6 (5.3)	–2.2 (5.4)	–0.1 (6.0)	–1.0 (6.9)	–2.0 (7.1)
Week 12	–1.3 (8.0)	0.4 (7.2)	–0.4 (6.5)	–0.0 (6.8)	–0.2 (7.1)	1.2 (6.6)	–2.7 (7.7)	–1.4 (6.3)	–2.3 (6.2)	–0.6 (6.1)	–1.4 (6.89)	–2.1 (6.8)
Week 24											NA	–1.4 (6.8)
Final on-treatment visit	–1.3 (7.9)	0.7 (7.0)	–0.5 (6.8)	–0.1 (6.7)	–0.6 (7.2)	0.9	–2.8 (7.7)	–1.3 (6.3)	–2.1 (6.1)	–0.5 (5.9)	–1.1 (6.76)	–1.5 (6.8)
Difference (SE) (95% CI)[b] **_P_ value**	–0.93 (0.64) (–2.20 to 0.33) *P* = 0.147		–0.56 (0.59) (–1.71 to 0.60) *P* = 0.346		–1.32 (0.82) (–2.93 to 0.29) *P* = 0.109		–1.53 (0.80) (–3.11 to 0.05) *P* = 0.058		1.32 (0.85) (–0.35 to 2.99) *P* = 0.121		–0.56 (0.67) (–1.88 to 0.75) *P* = 0.401	
Post-treatment												
Week 4	0.5 (7.1)		0.7 (6.2)	0.2 (7.5)	1.4 (6.0)	1.2 (6.4)	0.0 (6.5)		–1.2 (7.0)	1.0 (5.8)	0.60 (6.9)	–0.3 (7.2)
Week 12	1.4 (7.3)		0.8 (6.3)	0.6 (6.4)	1.7 (5.5)	1.5 (6.2)	0.8 (6.4)		0.5 (6.6)	0.6 (6.1)	0.5 (7.0)	0.9 (7.0)
Week 24	2.5 (7.3)		2.1 (4.4)	1.0 (7.3)	0.5 (n = 1)	–1.2 (2.0) (n = 2)	1.0 (6.1)		–2.8 (3.7)	–4.2 (13.3)		
Final post-treatment visit	1.4 (7.1)		0.8 (6.4)	0.5 (6.1)	1.7 (5.5)	1.5 (6.2)	0.9 (6.6)		0.3 (6.6)	0.5 (6.3)		

CI = confidence interval; NA = not applicable; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; PCS = physical component summary; RBV = ribavirin; SD = standard deviation; SE = standard error; SF-36 = Short-Form 36-Item Health Survey.
Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

TABLE 15: SUMMARY OF SHORT-FORM 36-ITEM HEALTH SURVEY MENTAL COMPONENT SCALE

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002)		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 88)	OBV/PTV/ RTV&DSV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/ RTV&DSV + RBV 24 Weeks (n = 172)
SF-36 MCS, mean (SD) change from baseline												
On-treatment												
Baseline	49.8	49.9	50.9	50.8	51.8	48.3	50.1	48.5	47.0	49.6	48.6	47.1
Week 4	–2.0 (8.2)	–1.1 (8.6)	–1.2 (7.4)	0.5 (7.0)	–1.6 (8.3)	1.5 (8.7)	–2.4 (7.9)	0.5 (7.6)	–2.2 (7.1)	–0.2 (9.3)	–0.5 (8.9)	–0.7 (8.7)
Week 8	–3.0 (9.0)	–1.7 (9.3)	–1.2 (7.7)	0.8 (7.7)	–2.8 (9.2)	1.1 (8.9)	–3.9 (9.4)	–0.5 (7.8)	–2.1 (7.7)	–0.6 (8.5)	–1.1 (9.8)	–1.8 (9.2)
Week 12	–3.7 (10.7)	–2.2 (10.2)	–1.3 (9.1)	–0.1 (9.1)	–2.5 (10.2)	0.5 (10.1)	–3.5 (9.6)	–0.6 (9.2)	–2.7 (8.5)	0.1 (8.7)	–2.4 (9.4)	–1.9 (9.3)
Week 24											NA	–2.8 (10.5)
Final on-treatment visit	–3.7 (10.5)	–2.0 (9.9)	–1.4 (9.2)	–0.1 (9.1)	–2.9 (10.6)	0.3 (10.1)	–3.7 (9.7)	–0.6 (9.0)	–2.4 (8.4)	0.1 (8.5)	–2.3 (9.4)	–2.9 (10.5)
Difference (SE) (95% CI) *P* value	–1.73 (0.92) (–3.55 to 0.09) P = 0.062		–1.17 (0.81) (–2.76 to 0.42) P = 0.150		–2.3 (1.22) (–4.70 to 0.10) P = 0.060		–2.71 (1.07) (–4.82 to –0.61) P = 0.012		2.81 (1.21) (0.42 to 5.21) P = 0.022		–1.03 (0.99) (–2.97 to 0.91) P = 0.296	
Post-treatment												
Week 4	0.3 (9.3)		0.6 (8.2)	1.4 (8.2)	–0.3 (7.5)	1.9 (10.8)	–0.3 (8.4)		0.2 (9.4)	1.5 (9.5)	1.1 (10.2)	–0.8 (9.3)
Week 12	2.0 (8.9)		1.3 (7.9)	1.5 (8.1)	1.3 (7.6)	2.4 (9.4)	0.8 (8.5)		1.8 (9.3)	2.0 (8.8)	0.5 (7.0)	0.9 (7.0)
Week 24	2.1 (7.5)		0.8 (5.1)	1.6 (8.1)	4.2 (n = 1)	–0.6 (7.7) (n = 2)	1.6 (8.4)		2.7 (7.6) (n = 8)	–3.7 (17.3) (n = 7)		
Final post-treatment visit	1.8 (9.4)		1.3 (7.9)	1.7 (7.7)	1.7 (5.5)	1.5 (6.2)	1.3 (8.7)		1.6 (9.4)	1.9 (9)		

CI = confidence interval; NA = not applicable; MCS = mental component summary; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; RBV = ribavirin; SD = standard deviation; SE = standard error; SF-36 = Short-Form 36-Item Health Survey.
Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

TABLE 16: SUMMARY OF EUROQOL 5-DIMENSIONS HEALTH INDEX SCORE

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002)		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/ RTV&DSV D + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 88)	OBV/PTV/ RTV&DSV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/ RTV&DSV + RBV 24 Weeks (n = 172)
EQ-5D health index score												
On-treatment												
Baseline	0.88	0.85	0.89	0.89	0.88	0.85	0.87	0.86	0.88	0.86	0.84	0.81
Week 4	–0.2 (0.1)	–0.01 (0.1)	–0.01 (0.1)	0.01 (0.1)	–0.02 (0.1)	0.00 (0.1)	–0.04 (0.1)	–0.01 (0.1)	–0.03 (0.1)	0.01 (0.10)	–0.02 (0.1)	–0.02 (0.1)
Week 8	–0.03 (0.1)	–0.01 (0.1)	–0.01 (0.1)	0.01 (0.1)	–0.04 (0.1)	0.01 (0.1)	–0.04 (0.1)	0.01 (0.1)	–0.02 (0.1)	0.01 (0.12)	–0.02 (0.1)	–0.02 (0.1)
Week 12	–0.02 (0.1)	–0.01 (0.1)	0.01 (0.11)	0.01 (0.1)	–0.04 (0.1)	–0.00 (0.1)	–0.04 (0.2)	–0.02 (0.1)	–0.03 (0.1)	–0.00 (0.1)	–0.03 (0.1)	–0.03 (0.1)
Week 24											NA	–0.02 (0.1)
Final on-treatment visit	–0.02 (0.1)	–0.01 (0.1)	0.0 (0.12)	0.01 (0.1)	–0.04 (0.1)	–0.00 (0.1)	–0.04 (0.2)	–0.02 (0.2)	–0.02 (0.1)	0.00 (0.1)	–0.03 (0.1)	–0.02 (0.1)
Difference (SE) (95% CI) *P* value	–0.001 (0.011) (–0.02 to 0.02) *P* = 0.961		–0.002 (0.012) (–0.025 to 0.020) *P* = 0.836		–0.028 (0.014) (–0.057 to 0.000) *P* = 0.052		–0.025 (0.016) (–0.057 to 0.006) *P* = 0.114		0.014 (0.015) (–0.016 to 0.044) *P* = 0.372		0.01 (0.014) (–0.02 to 0.03) *P* = 0.701	
Post-treatment												
Week 4	0.01 (0.1)	NR	0.01 (0.1)	0.01 (0.1)	0.00 (0.1)	0.01 (0.1)	–0.0 (0.1)	NR	–0.00 (0.1)	0.03 (0.1)	–0.01 (1.3)	–0.00 (0.1)
Week 12	0.01 (0.1)		0.01 (0.1)	0.02 (0.1)	–0.00 (0.1)	0.01 (0.1)	–0.01 (0.2)		0.01 (0.1)	0.01 (0.1)	–0.01 (0.1)	–0.00 (0.1)
Week 24	0.03 (0.1)		0.01 (0.1)	0.05 (0.1)	0.00 (n = 1)	–0.06 (0.1) (n = 2)	0.00 (0.1)		–0.0 (0.1)	–0.12 (0.2)		
Final post-treatment visit	0.02 (0.1)		0.01 (0.1)	0.02 (0.1)	–0.00 (0.1)	0.01 (0.1)	–0.00 (0.2)		0.01 (0.1)	0.01 (0.1)		

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; NA = not applicable; NR = not reported; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; RBV = ribavirin; SD = standard deviation; SE = standard error.
Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

TABLE 17: SUMMARY OF EUROQOL VISUAL ANALOGUE SCALE

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002)		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 88)	OBV/PTV/ RTV&DSV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/RTV &DSV + RBV 24 Weeks (n = 172)
EQ VAS score, mean (SD)												
On-treatment												
Baseline	81.2	78.9	82.5	83.7	82.6	80.3	79.0	78.6	79.3	79.1	76.1	73.0
Week 4	–2.1 (13.6)	–1.6 (13.5)	–1.1 (11.6)	0.4 (10.3)	–2.2 (15.2)	1.2 (11.9)	–3.8 (12.7)	–2.0 (12.0)	–2.1 (12.3)	1.7 (11.6)	–0.8 (12.9)	-0.8 (15.7)
Week 8	–2.6 (13.8)	–0.6 (12.0)	0.3 (12.0)	1.8 (10.2)	–1.5 (12.4)	2.7 (13.0)	–2.7 (13.7)	–0.6 (9.19)	–0.2 (10.8)	3.1 (12.8)	0.1 (16.2)	1.2 (15.4)
Week 12	–0.5 (15.0)	–0.5 (14.7)	2.6 (12.4)	1.5 (13.3)	0.5 (13.3)	3.6 (13.6)	–1.6 (14.9)	–1.1 (13.8)	–0.3 (12.4)	3.7 (11.3)	1.0 (15.2)	0.8 (15.0)
Week 24											NA	0.7 (17.1)
Final on-treatment visit	–0.6 (15.2)	–0.3 (14.1)	2.3 (13.4)	1.4 (13.3)	–0.0 (13.2)	3.5 (13.3)	–1.6 (15.1)	–1.1 (13. 6)	–0.2 (12.3)	3.4 (12.1)	0.8 (15.8)	0.6 (16.8)
Difference (SE) (95% CI)[b] *P* value	0.60 (1.3) (–1.88 to 3.08) *P* = 0.633		0.25 (1.14) (–1.98 to 2.48) *P* = 0.825		–2.73 (1.49) (–5.66 to 0.21) *P* = 0.068		–0.37 (1.6) (–3.56 to 2.82) *P* = 0.820		3.48 (1.72) (0.09 to 6.87) *P* = 0.044		–1.47 (1.504) (–4.42 to 1.49) *P* = 0.330	
Post-treatment												
Week 4	3.0 (15.2)		4.1 (11.8)	3.0 (11.5)	2.3 (10.4)	4.2 (12.3)	1.8 (14.5)	NR	2.0 (15.9)	6.6 (13.2)		
Week 12	4.6 (14.1)		4.0 (12.5)	3.6 (11.8)	4.3 (10.4)	5.4 (12.8)	4.3 (14.7)		5.1 (13.8)	5.2 (12.2)	3.86 (15.6)	5.23 (17.8)
Week 24	5.4 (13.0)		4.7 (7.9)	5.7 (14.8)	5.0 (n = 1)	–6.0 (12.7) (n = 2)	2.0 (11.0)		1.5 (11.3) (n = 8)	–10.5 (19) (n = 7)		
Final post-treatment visit												

CI = confidence interval; EQ VAS = EuroQol visual analogue scale; NA = not applicable; NR = not reported; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; RBV = ribavirin; SD = standard deviation; SE = standard error.
Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

TABLE 18: SUMMARY OF HEPATITIS C VIRUS PATIENT-REPORTED OUTCOMES INSTRUMENT

Outcome	Treatment-Naive Patients						Treatment-Experienced Patients				Mixed-Experience	
	SAPPHIRE I (M11-646)		PEARL III (M13-961)		PEARL IV (M14-002)		SAPPHIRE II (M13-098)		PEARL II (M13-389)		TURQUOISE II (M13-099)	
	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 473)	PBO 12 Weeks (n = 157)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 210)	OBV/PTV/ RTV&DSV + PBO 12 Weeks (n = 209)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 100)	OBV/PTV/RTV &DSV + PBO 12 Weeks (n = 205)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 297)	PBO 12 Weeks (n = 97)	OBV/PTV/RTV &DSV + RBV 12 Weeks (n = 88)	OBV/PTV/ RTV&DSV 12 Weeks (n = 91)	OBV/PTV/ RTV&DSV + RBV 12 Weeks (n = 208)	OBV/PTV/ RTV&DSV + RBV 24 Weeks (n = 172)
HCV-PRO score, mean (SD)												
On-treatment												
Baseline	79.5	77.3	81.1	82.9	80.8	76.5	77.4	78.1	77.2	77.3	74.4	70.5
Week 4	–2.4 (12.6)	0.2 (12.3)	–0.0 (13.8)	0.8 (10.0)	–2.3 (12.7)	1.4 (13.0)	–3.3 (13.2)	–1.2 (10.7)	–1.7 (13.2)	2.9 (12.1)	–1. 5 (13.2)	–0.5 (12.3)
Week 8	–4.5 (15.4)	0.2 (13.3)	0.1 (13.5)	0.7 (12.9)	–3.7 (14.3)	1.3 (13.6)	–4.8 (14.6)	1.0 (11.09)	–1.1 (12.3)	0.5 (13.2)	–1.1 (14.6)	–1.9 (14.4)
Week 12	–4.7 (17.1)	–1.3 (15.6)	0.6 (16.2)	0.2 (15.2)	–2.4 (15.0)	2.2 (15.6)	–4.1 (16.3)	–1.0 (11.8)	–2.3 (14.5)	1.4 (13.6)	–1.8 (15.0)	–2.2 (13.5)
Week 24											NA	–1.9 16.2
Final on-treatment visit	–4.8 (17.0)	–0.6 (14.5)	0.4 (16.7)	0.3 (15.0)	–3.3 (15.3)	1.9 (15.6)	–4.4 (16.5)	–0.9 (11.6)	–1.6 (14.6)	1.5 (13.4)	–1.8(14.9)	–2.0 (16.2)
Difference (SE) (95% CI)[b]	–3.61 (1.44) (–6.43 to –0.79)		–0.51 (1.43) (–3.32 to 2.30)		–4.31 (1.84) (–7.93 to –0.69)		–3.85 (1.74) (–7.28 to –0.43)		3.19 (2.04) (–8.84 to 7.21)		–1.1 (1.6) (–4.2 to 1.9)	
***P* value**	*P* = 0.012		*P* = 0.723		*P* = 0.020		*P* = 0.028		*P* = 0.120		*P* = 0.466	
Post-treatment												
Week 4	2.9 (15.9)	NR	4.3 (15.3)	3.4 (13.8)	4.8 (11.8)	4.9 (16.8)	2.2 (15.1)	NR	4.0 (16.0)	5.3 (14.1)		
Week 12	5.0 (15.3)		2.5 (9.2)	5.2 (12.9)	5.0 (12.2)	6.7 (16.1)	3.7 (14.8)		5.4 (15.9)	6.3 (13.4)	4.1 (13.1)	3.4 (15.2)
Week 24	6.1 (14.8)		8.6 (5.52) (n = 2)	4.7 (n = 1)	6.7 (n = 1)	2.3 (5.52) (n = 2)	5.1 (12.8)		11.4 (20.0)	–3.2 (27.8)		
Final post-treatment visit	4.8 (15.6)		4.3 (15.0)	3.1 (13.9)	5.1 (12.1)	6.6 (16.0)	4.2 (14.9)		6.0 (16.6)	6.5 (14.0)		

CI = confidence interval; HCV-PRO = Hepatitis C Virus Patient-Report Outcomes Instrument; NA = not applicable; NR = not reported; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; RBV = ribavirin; SD = standard deviation; SE = standard error.
Source: Clinical Study Reports: SAPPHIRE I (M11-646);[1] PEARL III (M13-961);[2] PEARL IV (M14-002);[3] SAPPHIRE II (M13-093);[4] PEARL II (M13-389);[5] TURQUOISE II (M13-099).[6]

APPENDIX 6: OTHER STUDIES OF INTEREST

Aim

To summarize the TURQUOISE I trial.[46] It was excluded from the systematic review because it was a phase 2 trial.

Findings

TURQUOISE I was planned in two major parts: part one is a phase 2 trial, and part two is a phase 3 trial. The first part of the trial was terminated and published, while part two has not yet been initiated. TURQUOISE I was designed to examine the safety and efficacy of OBV/PTV/RTV and DSV co-administered with RBV for 12 or 24 weeks in adults with genotype 1 CHC infection and HIV-1 co-infection, who were receiving a stable ART regimen inclusive of atazanavir or raltegravir plus two nucleos(t)ide analogue reverse transcriptase inhibitors for at least eight weeks before screening. The trial excluded patients who were co-infected with HBV or HIV type 2 (HIV-2), patients with decompensated cirrhosis, or patients who had experienced treatment failure with two or more ART regimens. Patients were not allowed to participate in the trial if they had any prior experience with direct-acting antiviral drugs.

Study Patients

Among patients randomized to Arm A (12-week treatment), 30 out of 31 completed treatment; one patient prematurely discontinued the study due to withdrawal of consent prior to treatment completion. Among the 32 patients randomized to Arm B (24-week treatment), 31 completed treatment; one patient prematurely discontinued study treatment due to on-treatment HCV virologic failure prior to treatment completion (rebound).

Demographic characteristics of the patients in Part 1a of the study are presented in Table 19. The majority of patients were male (92.1%). Additionally, 76.2% of patients reported being of Caucasian ethnicity, 23.8 % of patients reported being of black race, and 25.4% of patients reported Hispanic or Latino ethnicity.

TABLE 19: BASELINE CHARACTERISTICS IN TURQUOISE I

	OBV/PTV/RTV&DSV + RBV 12 Weeks (N = 31)	OBV/PTV/RTV&DSV + RBV 24 Weeks (N = 32)	Total (N = 63)
Age, mean (SD)	50.9 (6.0)	50.9 (8.3)	50.9 (7.2)
Male, n (%)	29 (93.5)	29 (90.6)	58 (92.1)
Race, n (%)			
Caucasian	24 (77.4)	24 (75.0)	48 (76.2)
Black	7 (22.6)	8 (25.0)	15 (23.8)
Genotype, n (%)			
HCV_1a	27 (87.1)	29 (90.6)	56 (88.9)
HCV_1b	4 (12.9)	3 (9.4)	7 (11.1)
IL28B_CC	5 (16.1)	7 (21.9)	12 (19.0)
IL28B_CT	16 (51.6)	20 (62.5)	36 (57.1)
IL28B_TT	10 (32.3)	5 (15.6)	15 (23.8)
Baseline HCV RNA, n (%)			
< 800,000 IU/mL	4 (12.9)	4 (12.5)	8 (12.7)

	OBV/PTV/RTV&DSV + RBV 12 Weeks (N = 31)	OBV/PTV/RTV&DSV + RBV 24 Weeks (N = 32)	Total (N = 63)
≥ 800,000 IU/mL	27 (87.1)	28 (87.5)	55 (87.3)
CD4 + T-cell count, mean (SD)	633.3 (235.6)	625.3 (296.0)	629.2 (265.9)
Presence of cirrhosis, n (%)			
Yes	6 (19.4)	6 (18.8)	12 (19.0)
No	25 (80.6)	26 (81.3)	51 (81.0)
Prior treatment status for HCV (PR)			
Treatment-naive	20 (64.5)	22 (68.8)	42 (66.7)
Treatment-experienced	11 (35.5)	10 (31.3)	21 (33.3)
Previous response to PR treatment			
Non-responder	5 (16.1)	5 (15.6)	10 (15.6)
Partial responder	5 (16.1)	2 (6.3)	7 (11.1)
Relapser	1 (3.2)	3 (9.4)	4 (6.3)

HCV = hepatitis C virus; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); PBO = placebo; PR = pegylated interferon and ribavirin; RNA = ribonucleic acid; SD = standard deviation.

Efficacy Results

For patients receiving the 12-week regimen, SVR12 was achieved by 29 of 31 (93.5%) patients. For patients treated with the 24-week regimen, SVR12 was achieved by 29 of 32 (90.6%) patients. Adverse events were high in both groups (90.3% and 87.5%). The trial did not conduct statistical comparisons between the two treatment groups, with each other, nor with a historical comparator.

Safety Results

Adverse events were reported at similar rates in the 12-week and 24-week arms (90% versus 88%); none of these adverse events were classified as serious. There were no adverse events leading to study discontinuation; however, some led to RBV dose reduction (16% versus 19% in the two arms, respectively). Common adverse events included fatigue (58% versus 38%), insomnia (16% versus 22%), nausea (16% versus 19%), headache (19% versus 13%), upper respiratory tract infection (13% versus 16%), pruritus (19% versus 6%), cough (7% versus 16%), ocular icterus (16% versus 3%), diarrhea (3% versus 13%), and hyperbilirubinemia (13% versus 3%).

TABLE 20: SUMMARY OF TURQUOISE I OUTCOMES

Outcome	OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 31)	OBV/PTV/RTV&DSV + RBV 24 Weeks (n = 32)
SVR12 (ITT population)		
N (%) [95% CI]	29 (93.5) [79.3 to 98.2]	29 (90.6) [75.8 to 96.8]
Difference (95% CI)		
HIV virologic response, N (%)		
Success	29 (93.5)	29 (90.6)
Failure	0	1 (3.1)
CD4 + T-cell percentage, mean (SD) change from baseline		
Baseline	31.1%	29.2%
Change from baseline	1.9% (2.8)	1.5% (3.5)

Outcome	OBV/PTV/RTV&DSV + RBV 12 Weeks (n = 31)	OBV/PTV/RTV&DSV + RBV 24 Weeks (n = 32)
Difference (SE)		
AEs		
Any AEs	28 (90.3)	28 (87.5)
Any SAEs	0	0
AEs leading to drug discontinuation	0	0
Deaths	0	0

AE = adverse event; CI = confidence interval; ITT = intention-to-treat; OBV/PTV/RTV&DSV = combination of direct-acting antiviral drugs (ombitasvir/paritaprevir/ritonavir and dasabuvir); RBV = ribavirin; SAE = serious adverse event; SD = standard deviation; SE = standard error; SVR12 = sustained virologic response for 12 consecutive weeks.

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