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CADTH COMMON DRUG REVIEW

Clinical Review Report

GLECAPREVIR / PIBRENTASVIR (MAVIRET)

(AbbVie Corporation)

Indication: Hepatitis C genotype 1 to 6

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

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Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ART	antiretroviral treatment
AST	aspartate aminotransferase
CHC	chronic hepatitis C
CI	confidence interval
DAA	direct-acting antiviral
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
EQ-5D-3L or -5L	EuroQol 5-Dimensions 3-Levels or 5-Levels questionnaire
GP	glecaprevir/pibrentasvir
HCV	hepatitis C virus
HRQoL	health-related quality of life
IFN	interferon
ITT	intention to treat
LLOQ	lower limit of quantitation
MCID	minimal clinically important difference
MCS	mental component summary
mITT	modified intention to treat
NS3/4A	nonstructural viral protein 3/4A
NS5A	nonstructural viral protein 5A
PCS	physical component summary
peg-IFN	pegylated interferon
PP	per-protocol
RCT	randomized controlled trial
RNA	ribonucleic acid
SF-36	Short Form (36) Health Survey
SVR	sustained virologic response
SVR 12	sustained virologic response at 12 weeks
ULN	upper limit of normal
VAS	visual analogue scale
WPAI-HCV	Work Productivity and Activity Impairment – Hepatitis C

Drug	Glecaprevir/pibrentasvir (Maviret)
Indication	For the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with a NS3/4A protease inhibitor but not both classes of inhibitors.
Reimbursement Request	As per indication
Dosage Form(s)	Glecaprevir (100 mg) / pibrentasvir (40 mg) tablet
NOC Date	August 16, 2017
Manufacturer	AbbVie Corporation

Executive Summary

Introduction

Hepatitis C virus (HCV) infection is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, hepatocellular carcinoma, liver failure, and hepatic encephalopathy. Patients report that symptoms are variable and, for some patients, the symptoms can be severe and limit their ability to work, manage their home, care for family members, and maintain relationships. In 2013, an estimated 250,000 Canadians had chronic HCV infection, but the exact number affected is not known, as 30% to 70% of patients are unaware they have been infected.[1]

Glecaprevir/pibrentasvir (GP) is a fixed-dose combination of two pan-genotypic direct-acting antiviral (DAA) agents: glecaprevir, an NS3/4A (nonstructural viral protein 3/4A) protease inhibitor; and pibrentasvir, an NS5A inhibitor. It is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with an NS3/4A protease inhibitor but not both classes of inhibitors.[2] The recommended dose is three glecaprevir 100 mg / pibrentasvir 40 mg tablets (i.e., 300 mg of glecaprevir and 120 mg pibrentasvir) once daily for 8, 12, or 16 weeks, depending on the patient's prior treatment experience and genotype, and cirrhosis is present.[2]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of a glecaprevir 100 mg / pibrentasvir 40 mg fixed-dose combination tablet for the treatment of chronic hepatitis C (CHC) genotype 1, 2, 3, 4, 5, and 6 infection in adults.

Results and Interpretation

Included Studies

A total of nine reports presenting data from 10 unique studies were included in the review. Three trials were open-label single-group studies (EXPEDITION-1, EXPEDITION-4, ENDURANCE-4) and four trials were open-label studies that randomized or assigned patients to more than one GP treatment group (ENDURANCE-1, SURVEYOR-II Part 3 and Part 4, MAGELLAN-1 Part 2). Two trials were open-label randomized controlled noninferiority trials (CERTAIN-2, ENDURANCE-3) and one trial was a randomized double-blind study (ENDURANCE-2).

Three trials (ENDURANCE-1, ENDURANCE-2, SURVEYOR-II Part 4) compared the percentage of patients who achieved a sustained virologic response 12 weeks after the end of treatment (SVR 12) for GP with a historical control to determine noninferiority. Two controlled trials were designed to assess the noninferiority of GP treatment for 8 weeks versus sofosbuvir/ribavirin treatment for 12 weeks (CERTAIN-2), or GP treatment for 12 weeks versus sofosbuvir/daclatasvir treatment for 12 weeks (ENDURANCE-3). The double-blind randomized controlled trial (RCT) ENDURANCE-2 was designed to assess safety of GP treatment for 12 weeks versus placebo.

Patients with all genotypes were enrolled including those who were treatment-naive (9 trials), had prior interferon (IFN)-based or sofosbuvir/ribavirin-based treatment experience (8 trials), prior DAA-treatment experience (1 trial), end-stage renal disease (ESRD) (1 trial) or HIV coinfection (1 trial). Patients with cirrhosis were included in three trials and those without cirrhosis were included in nine trials. In total, 2,180 patients received GP.

The mean age per treatment group ranged from 45.4 years to 60.1 years, and the patients enrolled were predominantly white (60% to 93%), except in CERTAIN-2 where all patients were Japanese. Most patients enrolled were fibrosis level F0 or F1 (median 76% per treatment group). The primary outcome in all trials was SVR 12.

The key limitation was the lack of comparative data, as eight of the 10 trials did not include another DAA-based regimen as a randomized control group. All but one of the studies were open label.

Efficacy

The percentage of patients achieving SVR 12 ranged from 88.6% to 99.7% among patients who received GP for 8, 12, or 16 weeks (Table 1).

In the ENDURANCE-1 study, the SVR 12 rate was 99.1% (95% confidence interval [CI], 98.1% to 100%) and 99.7% (95% CI, 99.1% to 100%) in non-cirrhotic genotype 1 patients in the GP 8-week and 12-week groups, respectively (modified intention-to-treat [mITT] population). GP 12 weeks met the noninferiority criteria as the lower bound of the 95% CI was greater than 91% for the historical control (ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin or sofosbuvir/ledipasvir for 12 weeks). GP 8 weeks was noninferior to GP 12 weeks as the lower limit of the 95% CI for the between-group difference was greater than the −5% noninferiority margin for the per-protocol (0.0%; 95% CI, −1.1% to 1.1%) and mITT (–0.6%; 95% CI, –1.8% to 0.6%) populations. GP 8 weeks is the Health Canada–recommended treatment duration for this study's population.

Among genotype 2 patients without cirrhosis (treatment-naive or had prior IFN-based therapy) who received GP for 12 weeks in the ENDURANCE-2 study, the SVR 12 rate was 99.5% (95% CI, 98.5% to 100%, mITT). GP for 12 weeks was noninferior to the historical control group (sofosbuvir/ribavirin 12 weeks) as the lower limit of the 95% CI was greater than 89% (i.e., 6% noninferiority margin). Of note, the treatment duration in ENDURANCE-2 was not consistent with the Health Canada–recommended duration of 8 weeks for this population.

CERTAIN-2 was designed to assess noninferiority of GP 8 weeks versus sofosbuvir /ribavirin 12 weeks in treatment-naive and treatment-experienced, non-cirrhotic patients with genotype 2 HCV infection. SVR 12 rates were 97.8% and 93.5% in the GP and sofosbuvir/ribavirin groups respectively, with a difference between treatments of 4.3% (95% CI, −3.5% to 12.1%). The lower bound of the 95% CI was above the −10% noninferiority margin; thus, GP 8 weeks was deemed noninferior to sofosbuvir/ribavirin based on the intention-to-treat (ITT) population. Limitations to this trial include a noninferiority margin that may be considered overly broad, and there was no evaluation of noninferiority using the per-protocol population, which may be a more conservative estimate. Moreover, external validity may be limited given that the study enrolled Japanese patients only, used a lower ribavirin dose than is used in Canada, and included an active control that may be considered suboptimal, based on current treatment standards.

In ENDURANCE-3, the percentage of treatment-naive, non-cirrhotic genotype 3 patients achieving SVR 12 was 96.5%, 95.3%, and 94.9% in the sofosbuvir /daclatasvir 12-week, GP 12 weeks, and GP 8 weeks groups, respectively. GP 12 weeks was noninferior to sofosbuvir/daclatasvir (SVR 12 difference: –1.2%; 95% CI, –5.6% to 3.1%, ITT) as the lower bound of the 95% CI was greater than the –6% noninferiority margin. Similar results were found for the per-protocol population. Superiority of GP 12 weeks versus sofosbuvir/daclatasvir was not met. GP 8 weeks also met the noninferiority criteria versus GP 12 weeks, based on the ITT and per-protocol analyses. Of note, patients in the GP 8-week group in the ENDURANCE-3 trial were not randomly assigned to the treatment; thus, there may be differences in measured and unmeasured confounders between the 12-week and 8-week groups. In addition, the ENDURANCE-3 trial did not evaluate the noninferiority of GP 8 weeks versus sofosbuvir/daclatasvir, which is the comparison of most interest, given that Health Canada recommends an 8-week treatment duration for the population enrolled.

In ENDURANCE-4, 99.2% (95% CI, 97.6% to 100%) of genotype 4, 5, or 6 patients achieved SVR 12 after 12 weeks of GP. One patient stopped treatment early and was considered a virologic failure. The Health Canada–recommended treatment duration is 8 weeks for these non-cirrhotic patients.

In SURVEYOR-II Part 3, the SVR 12 rate was 97.5% in treatment-naive cirrhotic genotype 3 patients. In treatment-experienced genotype 3 patients, the SVR 12 rate was 90.9% for non-cirrhotic patients who received GP for 12 weeks, and 95.5% and 95.7% in the non-cirrhotic and cirrhotic patients, respectively, who received 16 weeks of GP therapy. Health Canada recommends 16 weeks of treatment for treatment-experienced genotype 3 patients. Among the 22 treatment-experienced patients who received 12 weeks of therapy, two patients (9.1%) relapsed. In Part 4, treatment-naive and treatment-experienced non-cirrhotic patients received GP for 8 weeks. The SVR 12 rate was 97.9% (95% CI, 94.1% to 99.3%) in patients with genotype 2 HCV infection and 93.1% (95% CI, 83.6% to 97.3) in those with genotype 4 to 6 infection. Of the four patients with genotype 4 to 6 who

did not achieve SVR 12, one had discontinued treatment and three had missing SVR 12 data; none experienced an on-treatment virologic failure or relapse.

All patients in the EXPEDITION-1 study had compensated cirrhosis and genotype 1, 2, 4, 5, or 6 HCV infection. Overall, 99.3% of patients (95% CI, 98% to 100%) achieved SVR 12 after 12 weeks of GP. One patient experienced a relapse.

Among patients with ESRD, the SVR 12 rate was 98% (95% CI, 95% to 100%), and no patients in the EXPEDITION-4 study had an on-treatment virologic failure or relapse. Of the two patients who did not achieve SVR 12, one discontinued treatment early and one had missing SVR 12 data. Of note, 17% of the enrolled patients had cirrhosis and received the 12 weeks of GP treatment recommended by Health Canada. For non-cirrhotic patients, Health Canada recommends 8 weeks of therapy.[2]

In patients with genotype 1 or 4 CHC who had failed to respond to prior DAA-based therapy (MAGELLAN-1 Part 2), the SVR 12 rate was 88.6% (95% CI, 76.0% to 95.0%) in patients who received GP for 12 weeks, and 91.5% (95% CI, 80.1% to 96.6%) in those who received 16 weeks of treatment. There were more relapses in the 12-week group (n = 4, 9.3%) than the 16-week group (n = 0), although the total number of patients with on-treatment virologic failure or relapse was similar (12 weeks: n = 5, 11.4%; 16 weeks: n = 4, 8.5%). Of note, Health Canada recommends 12 weeks of GP in genotype 1 CHC patients (with or without cirrhosis) who have failed prior NS3/4A protease inhibitor treatment (simeprevir/sofosbuvir, or pegylated interferon plus ribavirin [PR] combined with simeprevir, boceprevir, or telaprevir) and who are NS5A inhibitor–naive.[2] Sixteen weeks of therapy is recommended for genotype 1 CHC patients with prior NS5A treatment experience (either daclatasvir/sofosbuvir, daclatasvir/PR or ledipasvir/sofosbuvir) and who are NS3/4A protease inhibitor–naive.GP is not recommended in patients who have been previously treated with a regimen of NS5A inhibitor with an NS3/4A protease inhibitor.[2] In the GP 12-week and 16-week groups, 32% and 38% patients, respectively, received the duration of treatment recommended by Health Canada.

Few patients experienced an on-treatment virologic failure or relapse (0 to 2 patients per group; < 1.5%) except for the study containing patients with prior DAA-treatment failure (MAGELLAN-1 Part 2) and the genotype 3 patients in the ENDURANCE-3 and SURVEYOR-II studies. In the ENDURANCE-3 study, six patients (3.8%) in the GP 8-week group and four patients (1.7%) in the GP 12-week group experienced a relapse or on-treatment virologic failure compared with one patient in the sofosbuvir/daclatasvir group (0.9%). In total, five of 90 (5.5%) treatment-experienced genotype 3 patients in SURVEYOR-II Part 3 experienced a relapse or on-treatment virologic failure; no treatment-naive genotype 3 patients relapsed. Other reasons for virologic failure were premature discontinuation of the study drug (0% to 2.2%) and missing SVR 12 data (0% to 5.2% across the treatment groups).

In MAGELLAN-1 Part 2, the SVR 12 rate in patients with NS3/4A- or NS5A-resistance variants present at baseline was 86%; it ranged from 91% to 95% in ENDURANCE-3 (genotype 3), and was 100% in other studies that reported these data.

All trials except MAGELLAN-1 evaluated patient-reported outcomes as exploratory outcomes. The instruments used included the Short Form (36) Health Survey (SF-36) (seven trials), the EuroQol 5-Dimensions questionnaire (EQ-5D) (nine trials), the Fatigue Severity Scale (FSS) (eight trials), and the Work Productivity and Activity Impairment – Hepatitis C (WPAI-HCV) (seven trials). Between-group statistical comparisons were conducted in the ENDURANCE-2, ENDURANCE-3, and CERTAIN-2 studies; however,

no statistically significant differences were detected between GP and placebo, sofosbuvir/daclatasvir or sofosbuvir/ribavirin for the instruments tested. Patient-reported outcomes reported in these and the other trials were difficult to interpret due to limitations in the data, including the open-label design, missing data, the analysis methods used (i.e., no imputation of missing data or control of multiplicity), or lack of a control group.

The key limitation of the available evidence was the lack of comparative data, as eight of the 10 trials did not include another DAA-based regimen as a randomized control group. Six of the 10 studies were uncontrolled or assigned some patients to groups non-randomly. ENDURANCE-1, ENDURANCE-2, and SURVEYOR-II Part 4 share the same limitations related to comparisons with a historical control, rather than a direct comparison between trial arms, which limits the ability to assess differences between the randomized treatments because of possible changes in clinical practice (i.e., standard of care), and the characteristics of the patient populations from different time periods may not be similar. Moreover, three of the trials selected sofosbuvir/ribavirin as a historical or concurrent control group and this regimen may be considered suboptimal by today's treatment standards, although, at the time the trials were designed, sofosbuvir/ribavirin may have been the accepted standard of care.[3,4] Importantly there were no data comparing GP with the other pan-genotypic DAA regimens that are commonly used in Canada (e.g., sofosbuvir/velpatasvir [Epclusa] or sofosbuvir/ledipasvir [Harvoni]), although this may not have been feasible given the rapid pace of development of treatments for hepatitis C.

Overall, the trials represent a chronic HCV population with less severe liver fibrosis, as fewer than 20% had advanced fibrosis or cirrhosis in most studies. Generalizability of trial results may be limited for some patient groups, as more complex patients with important concurrent conditions were listed as exclusion criteria in the trials. For example, patients with HIV coinfection were excluded from all but one pivotal trial. No patients who had undergone a transplant were included in the pivotal trials, although there is one non-pivotal uncontrolled study in this population.[5] Patients with ESRD were included in one study. Few patients with genotype 5 and 6 HCV infection, genotype 3 and treatment experience, or with prior DAA-treatment experience were enrolled.

Harms

In general, the majority of patients experienced one or more adverse events with headache, fatigue, and nausea reported most frequently among those who received GP. In the double-blind placebo-controlled trial, 65% and 58% of patients reported adverse events in the GP and placebo groups, respectively (ENDURANCE-2). Overall, 76%, 62%, and 70% of patients in the GP 12-week, GP 8-week, and sofosbuvir/daclatasvir 12-week groups respectively, reported an adverse event in the ENDURANCE-3 RCT. In the CERTAIN-2 RCT, 76% versus 48% of patients reported an adverse event in the sofosbuvir/ribavirin versus GP groups, respectively, with anemia (35% versus 0%) and increased bilirubin (15.2% versus 1.1%) reported more frequently for sofosbuvir/ribavirin-treated patients. The duration of treatment however, was longer for sofosbuvir/ribavirin (12 weeks) than GP (8 weeks), which may account for some differences in frequency.

The frequency of serious adverse events was highest (24%) in patients with ESRD, most of whom were undergoing dialysis, and those in EXPEDITION-1 (7.5%), which only enrolled patients with compensated cirrhosis. Unfortunately, neither of the studies had a control group; thus, it is not possible to determine to what extent the serious adverse events were related to the study drug or to the patients' underlying medical condition. In the other studies, the frequency of serious adverse events among GP-treated patients ranged from

0.8% to 4.6%, and was similar for GP and placebo or daclatasvir/sofosbuvir in ENDURANCE-2 and -3. In total, four deaths occurred among the 2,180 patients who received GP. One death was reported among patients who received sofosbuvir/daclatasvir (total N = 115); no deaths were reported among those who received placebo or sofosbuvir/ribavirin (N = 146). Two deaths were due to cerebral hemorrhage, one was an accidental overdose, and two had an unknown cause. Hepatic-related toxicity or morbidity events were infrequent and generally occurred in patients with more severe liver disease at baseline. In all treatment groups, few patients stopped treatment due to adverse events (0% to 3.8%). Withdrawals were highest in the trial in patients with ESRD (3.8%).

The two supporting studies in patients who had undergone a liver or kidney transplant or those with HIV coinfection showed a similar adverse event profile as the studies included in the systematic review.

Of the included trials, only ENDURANCE-2 was double blinded; thus, the reporting of adverse events may be influenced by the patient's knowledge of the treatment received. The lack of an active control group in most of the studies is an important limitation of the available safety data, as comparative data are scarce. Moreover, the trials were not designed to assess the longer-term safety of GP. All of the trials excluded patients with hepatitis B coinfection; thus, the trials provide no data on the risk of hepatitis B reactivation, which is listed as a warning on the product monograph.[2] GP also has a number of potentially clinically important drug–drug interactions, which may affect the risk of adverse effects or reduce the therapeutic effect of GP.[2]

Potential Place in Therapy[1]

GP is a ribavirin-free, pan-genotypic regimen that provides overall sustained virologic response (SVR) rates of greater than 95% to 98% in almost all patients with HCV. In the opinion of the clinical expert consulted by CADTH, this regimen showed a similar adverse event profile when compared with placebo.[6]

GP is a pan-genotypic option with an eight-week treatment duration in treatment-naive patients without cirrhosis. This patient group likely accounts for 80% of the HCV patients who remain to be treated. As such, it offers the ability to change the treatment paradigm to treating for eight weeks in the majority of patients who otherwise would require 12 weeks of treatment with most other DAA regimens currently available. Cirrhotic patients would require a 12-week course similar to other pan-genotypic regimens, and some treatment-experienced patients may require up to 16 weeks of therapy. All patients with HCV need to be evaluated for fibrosis stage, as those with cirrhosis require long-term monitoring for hepatocellular carcinoma. Similarly, all health care providers, regardless of their level of experience, should ensure that all their HCV patients are evaluated for fibrosis stage.

Because GP is eliminated through the biliary-fecal route, it is the only pan-genotypic regimen approved by Health Canada for patients with renal disease who have an estimated glomerular filtration (eGFR) rate of ≤ 30 mL/min., or who are on dialysis. Another potential differentiating attribute of GP is that it provides a different option in the context of drug–drug interactions, which may be important in various clinical settings.

In the treatment of HCV, baseline resistance testing has been suggested by international guidelines depending on the regimen, genotype, fibrosis level, or if prior-treatment

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

experienced.[3,4] This has been a particular issue with certain genotype 3 patients. At present, baseline resistance testing is not needed for GP, unless re-treating DAA-experienced patients. It is very uncommon for patients to fail the presently reimbursed DAA regimens. However, 3% to 10% may fail the first DAA regimen.[7-9] In this population it is important to consider the prior DAA regimen and obtain a baseline resistance evaluation to guide re-treatment. These patients should be treated by or in conjunction with centres experienced with this challenging patient profile. GP is approved only for the re-treatment of genotype 1 patients, though those who are NS5A experienced or have a baseline NS5A resistance-associated variant have a lower SVR. Other DAA re-treatment options would include the recently approved sofosbuvir/ velpatasvir/ voxilaprevir.

As with other regimens that contain protease inhibitors, GP must not be used by patients whose liver disease is classified as Child-Pugh class B or C, or patients with a MELD (Model for End-Stage Liver Disease) score greater than 6.

GP is a welcome addition in HCV therapeutics, providing patients with a pan-genotypic option that is highly efficacious, seemingly well tolerated, and easy to utilize. It is hoped with screening and linkage to care, and with the multiple DAA regimens now available, we will be able to realize in Canada the World Health Organization goal of eliminating HCV by 2030.[10]

Conclusions

Treatment with GP for 8, 12, or 16 weeks was associated with a high percentage of patients achieving SVR 12, with point estimates that ranged from 90.9% to 99.7% in adults with HCV infection genotype 1 to 6 who were treatment-naive, had previously received IFN- or sofosbuvir/ribavirin-based treatment, or had ESRD. The percentage of DAA treatment–experienced, genotype 1 patients who achieved SVR 12 was 88.6% and 91.5% among those who received GP for 12 or 16 weeks, respectively.

GP for 12 weeks was noninferior to sofosbuvir/daclatasvir in treatment-naive, non-cirrhotic patients with genotype 3 HCV infection, although the relevance of this finding is unclear given that eight weeks is the approved duration for GP in this population. GP treatment for eight weeks was also noninferior to sofosbuvir/ribavirin 12 weeks in non-cirrhotic treatment-naive and prior IFN-based treatment-experienced patients with genotype 2 HCV infection; however, the external validity of these findings may be limited given that the study enrolled only Japanese patients, used a lower ribavirin dose than is used in Canada, and included an active control that may be considered suboptimal based on current treatment standards. In non-cirrhotic genotype 1 HCV patients (treatment-naive or prior IFN-based therapy), GP 8 weeks was noninferior to GP 12 weeks.

Health-related quality of life, fatigue, and work productivity were evaluated as exploratory outcomes using the SF-36, EQ-5D, FSS, and the Work Productivity and Activity Index – Hepatitis C instruments. No conclusions could be drawn for these outcomes due to limitation in the data that included open-label study design, missing data, analysis methods used, or lack of a control group. Headache, fatigue, and nausea were reported most frequently among those who received GP. None of the trials were designed to assess longer-term outcomes, such as hepatic-related morbidity or mortality, which are important to patients.

The key limitation was the limited comparative data, as eight of the 10 trials did not include another DAA-based regimen as a randomized control group, or the comparator selected (i.e., sofosbuvir/ribavirin) was considered suboptimal according to current clinical guidelines. In particular, there were no comparative data for sofosbuvir/velpatasvir, another pan-genotypic DAA-based regimen that is approved in Canada and has been reviewed by the CADTH Common Drug Review. Six of the 10 studies included in this review were uncontrolled or assigned some patients to groups non-randomly. Patients with more complex care needs (i.e., with important concurrent conditions) were excluded from the trials; thus, generalizability of the studies' findings to these patients may be limited. Data were scarce for patients with HIV coinfection, liver transplants, genotype 5 and 6 HCV infection, genotype 3 with treatment experience, or those with prior DAA-treatment experience.

Table 1: Summary of Results

Study/Treatment	Population[a]	N[b]	SVR 12 % (95% CI)	On-Treatment Virologic Failure n (%)	Relapse n (%)	SAE n (%)
ENDURANCE-1						
GP 8 weeks[c]	G 1 TN/IFN NC	335	99.1 (98.1–100)	1 (0.3)	0	5 (1.4)
GP 12 weeks	G 1 TN/IFN NC	332	99.7 (99.1–100)	0	0	4 (1.1)
ENDURANCE-2						
GP 12 weeks	G 2 TN/IFN NC	196	99.5 (98.5–100)	0	0	3 (1.5)
Placebo	G 2 TN/IFN NC	100	NA	NA	NA	1 (1.0)
ENDURANCE-3						
GP 12 weeks	G 3 TN NC	233	95.3 (92.6–98.0)[d]	1 (0.4)	3 (1.4)	5 (2.1)
SOF/DCV 12 weeks	G 3 TN NC	115	96.5 (93.2–99.9)	0	1 (0.9)	2 (1.7)
GP 8 weeks[c]	G 3 TN NC	157	94.9 (91.5–98.3)	1 (0.6)	5 (3.3)	3 (1.9)
ENDURANCE-4						
GP 12 weeks	G 4, 5, 6 TN/TE NC	121	99.2 (97.6–100)	0	0	1 (0.8)
CERTAIN-2						
GP 8 weeks[c]	G 2 TN/TE NC	90	97.8 (94.7–100)[e]	0	0	2 (2.2)
SOF/RBV 12 weeks	G 2 TN/TE NC	46	93.5 (86.3–100)	0	2 (4.4)	2 (4.3)
SURVEYOR-II Part 3						
GP 12 weeks	G 3 TE NC	22	90.9 (72.2–97.5)	0	2 (9.1)	2 (4.5)
GP 16 weeks[c]	G 3 TE NC	22	95.5 (78.2–99.2)	0	1 (4.5)	
GP 12 weeks[c]	G 3 TN C	40	97.5 (87.1–99.6)	0	0	4 (4.6)
GP 16 weeks[c]	G 3 TE C	47	95.7 (85.8–98.8)	1 (2.1)	1 (2.2)	

Study/Treatment	Population[a]	N[b]	SVR 12 % (95% CI)	On-Treatment Virologic Failure n (%)	Relapse n (%)	SAE n (%)
SURVEYOR-II Part 4						
GP 8 weeks[c]	G 2 TN/TE NC	145	97.9 (94.1–99.3)	0	2 (1.4)	2 (1.0)
GP 8 weeks[c]	G 4, 5, 6 TN/TE NC	58	93.1 (83.6–97.3)	0	0	
EXPEDITION-1						
GP 12 weeks[c]	G 1, 2, 4, 5, 6 TN/TE C	146	99.3 (98.0–100)	0	1 (0.7)	11 (7.5)
EXPEDITION-4						
GP 12 weeks	G 1–6 ESRD TN/TE C/NC	104	98.1 (95.4–100)	0	0	25 (24.0)
MAGELLAN-1 Part 2						
GP 12 weeks	G 1, 4, 5, 6 DAA-TE C/NC	44	88.6 (76.0–95.0)	1 (2.3)	4 (9.3)	1 (2.3)
GP 16 weeks	G 1, 4, 5, 6 DAA-TE C/NC	47	91.5 (80.1–96.6)	4 (8.5)	0	2 (4.3)

C = cirrhosis; CI = confidence interval; DAA = direct-acting antiviral; DCV = daclatasvir; ESRD = end-stage renal disease; G = genotype; GP = glecaprevir/pibrentasvir; INF = interferon; NA = not applicable; NC = no cirrhosis; NS = nonstructural viral protein; IFN = interferon; ITT = intention to treat; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir; SVR 12 = sustained virologic response at 12 weeks; TE = treatment-experienced; TN = treatment-naive.

[a] TE refers to prior IFN or peg-IFN ± RBV or SOF + RBV ± peg-IFN. IFN refers to prior IFN or peg-IFN ± RBV. DAA-TE refers to inadequate response to an NS5A inhibitor (limited to DCV, ledipasvir, or ombitasvir) or an NS3/4A inhibitor (paritaprevir/ritonavir, simeprevir, telaprevir, boceprevir regimens).

[b] ITT population except for ENDURANCE-1, which excluded patients with HIV coinfection or prior SOF/RBV ± peg-IFN treatment, and ENDURANCE-2, which excluded patients with prior SOF/RBV ± peg-IFN failure.

[c] All patients in the GP group received the Health Canada–recommended treatment duration.

[d] GP 12 weeks was noninferior to SOF/DCV 12 weeks based on a –6% noninferiority margin (SVR 12 difference ITT: –1.2% [95% CI, –5.6% to 3.1%]; PP: –1.7% [95% CI, −5.1% to 1.7%]).

[e] GP 8 weeks noninferior to SOF/RBV 8 weeks based on a 10% noninferiority margin (SVR 12 difference ITT: 4.3% [95% CI, –3.5 to 12.1%, PP: not reported]).

Source: Clinical Study Reports.[6,11-18]

Introduction

Disease Prevalence and Incidence

Hepatitis C virus (HCV) infection is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, hepatocellular carcinoma, liver failure, and hepatic encephalopathy. It is caused by an enveloped, single-stranded linear ribonucleic acid (RNA) virus of the Flaviviridae family. In 2013, an estimated 250,000 Canadians had chronic HCV infection, but the exact number affected is not known, as 30% to 70% of patients are unaware they have been infected.[1] A total of 10,180 new cases of HCV were reported in Canada in 2012, mostly due to injection drug use.[19] Hepatitis C most commonly affects people who are older than 30 years of age, and disproportionately men, although the gender gap is narrowing.[19] Other populations at higher risk for HCV infection include federal inmates, men who have sex with men, street-involved youth, and Indigenous people.[20] There are six major HCV genotypes, of which genotype 1 infections are the most common in Canada (65%).[1] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, respectively.[1] Genotypes 4, 5, and 6 are less common in Canada and account for less than 1% of HCV cases.[1]

Of those infected, approximately 25% clear the infection spontaneously (range 15% to 45%) and the remainder develop chronic infection.[21-23] Of those with chronic infection, 15% to 25% will develop progressive liver disease, end-stage liver disease, or hepatocellular carcinoma, or will require a liver transplant.[24] Male gender, alcohol use, HIV or hepatitis B coinfection, obesity, and increasing age are associated with an increased risk of liver disease progression.[3,24] While the incidence of HCV infection appears to be stable or declining in Canada (increased incidence in some areas of US), it is expected that liver-related morbidity and mortality will continue to increase over the coming decades, as those who are already infected age.[1,19,25-27] Patient groups report that the degree to which symptoms affect individuals is variable, ranging from no symptoms or minor symptoms, to severe symptoms that can limit a patient's ability to work, manage their home, care for family members, and maintain relationships.

Standards of Therapy

The treatment paradigm for HCV infection continues to evolve rapidly. Ongoing development of new direct-acting antiviral (DAA) agents have brought a number of drugs to market in Canada (Table 3), including the first pan-genotypic regimen velpatasvir plus sofosbuvir (Epclusa).[2,28-35] The combination of ledipasvir and sofosbuvir (Harvoni) also has approval for genotype 1 to 6 HCV infection, as well as for adult liver-transplant recipients or those with HIV coinfection (genotype 1 and 4), and genotype 1 patients with decompensated cirrhosis.[30] Other available drugs include elbasvir plus grazoprevir (Zepatier) which may be used in patients with genotype 1 or 4 HCV infection, or in combination with sofosbuvir in patients with genotype 3 infection.[35] Ombitasvir/paritaprevir/ritonavir (Technivie) is approved to treat genotype 4 chronic hepatitis C (CHC) and is combined with dasabuvir for genotype 1 CHC (Holkira Pak).[31,34] Also available is asunaprevir (Sunvepra) and daclatasvir (Daklinza) for patients with genotype 1b HCV infection, or daclatasvir with sofosbuvir for those with genotype 1, 2, or 3 infection.[28,33] In the April 2017 update to the Infectious Disease Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) guidelines, interferon (IFN)-based and pegylated interferon (peg-IFN)-based treatment regimens; the first-generation nonstructural protein 3/4A

(NS3/4A) protease inhibitors (boceprevir, telaprevir, and simeprevir with peg-IFN/ribavirin); and sofosbuvir/ribavirin were no longer recommended.[3]

The two most recently approved regimens, glecaprevir/pibrentasvir (GP) and sofosbuvir/velpatasvir/voxilaprevir, are both pan-genotypic. Sofosbuvir/velpatasvir/voxilaprevir is approved for use in patients who are DAA treatment–experienced with regimens containing an NS5A inhibitor (genotype 1 to 6); or with sofosbuvir without an NS5A inhibitor (genotype 1 to 4).[36] The IDSA/AASLD guidelines include GP as a recommended treatment option for treatment-naive patients with genotype 1 to 6 HCV infection and for select treatment-experienced patients.[37]

Although there are several recommended treatment options for patients with genotype 1 HCV infection, the available options are more limited for other patient populations, such as those with genotype 5 or 6 HCV infection or severe renal impairment, or who have failed to respond to a DAA-based regimen.[37] Several treatments for HCV infection are contraindicated in those with decompensated liver disease, but now there are treatments available, including: velpatasvir/sofosbuvir/ribavirin for all genotypes; ledipasvir/sofosbuvir for genotype 1 HCV infection; and daclatasvir/sofosbuvir/ribavirin for genotype 1, 2, or 3. Regimens containing protease inhibitors are not to be used in patients with Child-Pugh class B or C cirrhosis. DAA treatment options exist for liver-transplant recipients as well as those with HIV coinfection, although drug–drug interactions must be taken into consideration when selecting HCV treatments for these patients.[3] The presence of drug-resistant viral variants needs to be considered in some subsets of patients who are being considered for treatment with elbasvir and grazoprevir.[3]

Drug

GP is a fixed-dose combination of two pan-genotypic DAAs: glecaprevir, an NS3/4A protease inhibitor; and pibrentasvir, an NS5A inhibitor. It is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with a regimen containing either an NS5A inhibitor or an NS3/4A protease inhibitor, but not with both classes of inhibitors.[2]

Each tablet contains 100 mg of glecaprevir and 40 mg of pibrentasvir, and the recommended dose is three tablets (300 mg/120 mg) once daily for eight, 12, or 16 weeks, depending on the patient's prior treatment experience and genotype and whether cirrhosis is present (Table 2).[2]

GP is contraindicated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended in patients with moderate hepatic impairment (Child-Pugh class B). The product monograph states that the safety and efficacy of GP in post–liver transplant patients has not been established, and that safety and efficacy has not been fully established in patients with HIV coinfection.[2].

Table 2: Treatment Duration for Glecaprevir/Pibrentasvir

Population[a]	HCV Genotype	Treatment Duration	
		Without Cirrhosis	With Cirrhosis
Treatment-naive	1, 2, 3, 4, 5, 6	8 weeks	12 weeks
Treatment-experienced			
PR and/or SOF/RBV[b]	1, 2, 4, 5, or 6	8 weeks	12 weeks
PR and/or SOF/RBV[b]	3	16 weeks	16 weeks
NS3/4A PI[c] (NS5A inhibitor–naive)	1	12 weeks	12 weeks
NS5A[d] (NS3/4A inhibitor–naive)	1	16 weeks	16 weeks

HCV = hepatitis C virus; NS = nonstructural viral protein; PI = protease inhibitor; PR = pegylated interferon plus ribavirin; RBV = ribavirin; SOF = sofosbuvir.
[a] Includes patients with HCV mono-infection or HIV-1 coinfection, with compensated liver disease (with or without cirrhosis) and with or without renal impairment including those receiving dialysis.
[b] Experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir (PR, SOF + PR, SOF + RBV, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.
[c] Experienced with regimens containing simeprevir + SOF or simeprevir + PR or boceprevir + PR or telaprevir + PR.
[d] Regimens containing daclatasvir + SOF, daclatasvir + PR, ledipasvir + SOF.
Source: Product monograph.[2]

Table 3: Key Characteristics of DAAs Approved for Use in Canada

Drug (Brand Name)	Mechanism of Action	Health Canada Indication	Serious Adverse Effects / Safety Issues
Sofosbuvir (Sovaldi)	HCV NS5B polymerase inhibitor. The NS5B polymerase is a RNA polymerase that is critical for the viral replication cycle.	Treatment of genotype 1, 2, 3, or 4 CHC infection as a component of a combination antiviral treatment regimen.[a]	Fatigue, headache, insomnia
Sofosbuvir/ Ledipasvir (Harvoni)	Ledipasvir is an HCV NS5A inhibitor. The NS5A protein is an essential component of HCV replicase even though no known enzymatic function has been associated with it. Sofosbuvir is an NS5B polymerase inhibitor.	Treatment of CHC infection genotype 1 to 6 in adults with and without cirrhosis including: • genotype 1 and 4 CHC infection in adult liver-transplant recipients without cirrhosis, or with compensated cirrhosis in combination with ribavirin • genotype 1 and 4 CHC infection in adults with HIV coinfection, without cirrhosis or with compensated cirrhosis • genotype 1 CHC infection in adult patients with decompensated cirrhosis (Child-Pugh B or C) in combination with ribavirin • genotype 3 CHC without cirrhosis or with compensated cirrhosis in combination with ribavirin • genotype 1, 2, 4, 5, and 6 without cirrhosis or with compensated cirrhosis. Treatment of CHC genotype 1 infection in pediatric patients ≥ 12 years of age, without cirrhosis or with compensated cirrhosis.	Fatigue, headache

Drug (Brand Name)	Mechanism of Action	Health Canada Indication	Serious Adverse Effects / Safety Issues
Sofosbuvir/ Velpatasvir (Epclusa)	Velpatasvir is an HCV inhibitor targeting the HCV NS5A protein Sofosbuvir is an NS5B polymerase inhibitor.	Treatment of all HCV genotypes in adult patients without cirrhosis and patients with compensated cirrhosis. Treatment of all HCV genotypes in adult patients with decompensated cirrhosis in combination with ribavirin.	Headache and fatigue
Daclatasvir (Daklinza)	Inhibitor of the NS5A replication complex.	Treatment of CHC in adult patients with HCV genotypes 1, 2, or 3, with or without HIV coinfection, in combination with: • sofosbuvir for patients without cirrhosis • sofosbuvir and ribavirin for patients with compensated (Child-Pugh Class A) or decompensated cirrhosis (Child-Pugh Class B and C) • sofosbuvir and ribavirin for patients with HCV recurrence after liver transplant.	Headache and fatigue
Asunaprevir (Sunvepra)	HCV NS3/4A serine protease inhibitor which inhibits viral replication.	Treatment of CHC in adult patients with HCV genotypes 1 or 4 and compensated liver disease, including cirrhosis in combination with: • daclatasvir for genotype 1b HCV • daclatasvir, pegylated interferon alfa and ribavirin for genotype 1 and 4 HCV.	Headache and fatigue
Ombitasvir/ paritaprevir/ ritonavir and dasabuvir (Holkira Pak)	• Ombitasvir: HCV NS5A inhibitor that inhibits viral replication. • Paritaprevir: HCV NS3/4A protease inhibitor that inhibits viral replication. • Dasabuvir: non-nucleoside polymerase inhibitor encoded by the NS5B gene that is essential for replication of the viral genome. • Ritonavir: pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir. It is not active against HCV.	Treatment of adults with genotype 1 chronic HCV[a] infection including those with compensated cirrhosis: • with ribavirin in non-cirrhotic and cirrhotic patients with genotype 1a infection • without ribavirin in non-cirrhotic and cirrhotic patients with genotype 1b infection.	Fatigue, headache, nausea, pruritus and insomnia
Ombitasvir/ paritaprevir/ ritonavir (Technivie)	• Ombitasvir: HCV NS5A inhibitor which inhibits viral replication. • Paritaprevir: HCV NS3/4A protease inhibitor, which inhibits viral replication. • Ritonavir: pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir. It is not active against HCV.	Alone or in combination with ribavirin for the treatment of adults with genotype 4 CHC virus infection, including those with compensated cirrhosis, who are either treatment-naive or previously treated with PR.	Fatigue, headache, nausea, pruritus, and insomnia

Drug (Brand Name)	Mechanism of Action	Health Canada Indication	Serious Adverse Effects / Safety Issues
Elbasvir/ grazoprevir (Zepatier)	• Elbasvir is an HCV NS5A inhibitor. • Grazoprevir is an HCV NS3/4A protease inhibitor.	• Alone or in combination with ribavirin for the treatment of CHC genotypes 1 or 4 infection in adults. • In combination with sofosbuvir for the treatment of CHC genotype 3 infection in treatment-naive adult patients.	Nausea, headache, and fatigue
Sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi)	• Velpatasvir is an HCV NS5A inhibitor. • Voxilaprevir is an NS3/4A protease inhibitor. • Sofosbuvir is an NS5B polymerase inhibitor.	For the treatment of CHC in adult patients, without cirrhosis or with compensated cirrhosis, who have: • genotype 1, 2, 3, 4, 5, or 6 infection and have been treated previously with an HCV regimen containing an NS5A inhibitor • genotype 1, 2, 3, or 4 infection and have been treated previously with an HCV regimen containing sofosbuvir without an NS5A inhibitor.	Headache, fatigue, diarrhea, and nausea
Glecaprevir/ pibrentasvir (Maviret)	Glecaprevir is an NS3/4A protease inhibitor and pibrentasvir is an NS5A inhibitor.	For the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections with or without compensated cirrhosis. This includes patients with HCV genotype 1 infection who were previously treated with either a regimen of NS5A inhibitor or with an NS3/4A protease inhibitor but not with both classes of inhibitors. (Includes patients with HIV coinfection.)	Headache, fatigue

CHC = chronic hepatitis C virus; DAA = direct-acting antiviral; HCV = hepatitis C virus; NS = nonstructural viral protein; PR = pegylated interferon plus ribavirin; RNA = ribonucleic acid.

[a] Includes patients with HIV coinfection or those who have undergone a liver transplant.

Source: Product monographs.[2,28-35]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of the glecaprevir 100 mg / pibrentasvir 40 mg fixed-dose combination tablet for the treatment of CHC genotype 1, 2, 3, 4, 5, and 6 infection in adults.

Methods

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

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adults with CHC genotype 1 through 6. Subpopulations: • treatment history (treatment-naive, treatment-experienced [i.e., interferon-based therapy or DAA therapy]) • fibrosis level • cirrhosis • HIV coinfection • hepatitis B coinfection • genotype • genotype subtype 1a or 1b • renal insufficiency • liver transplant • decompensated liver disease • HCV RNA levels

Intervention	Glecaprevir 300 mg / pibrentasvir 120 mg once daily as follows[a]:
	• treatment-naive genotype 1 through 6
	  • without cirrhosis (8 weeks)
	  • with cirrhosis (12 weeks)
	• treatment-experienced
	  • genotype 3 (16 weeks)
	  • NS5A inhibitor–naive genotype 1, 2, 4, 5, or 6 without cirrhosis (8 weeks) or with cirrhosis (12 weeks)[b]
	  • NS5A inhibitor-experienced genotype 1, 2, 4, 5, or 6, with or without cirrhosis (16 weeks)[c]
	• prior liver transplant (12 weeks)

Comparators[d]	**Genotype 1:** • ledipasvir/sofosbuvir[e] • ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavirin • daclatasvir/sofosbuvir ± ribavirin • asunaprevir/daclatasvir for genotype 1b • sofosbuvir/velpatasvir • elbasvir/grazoprevir ± ribavirin • placebo or no treatment **Genotype 2:** • ledipasvir/sofosbuvir • sofosbuvir/velpatasvir • Sofosbuvir/ribavirin • daclatasvir/sofosbuvir ± ribavirin

	• placebo or no treatment **Genotype 3:** • ledipasvir/sofosbuvir plus ribavirin • sofosbuvir/velpatasvir • sofosbuvir/ribavirin • daclatasvir/sofosbuvir ± ribavirin[a] • elbasvir/grazoprevir/sofosbuvir (treatment-naive patients) • placebo or no treatment **Genotype 4:** • ledipasvir/sofosbuvir[e] • ombitasvir/paritaprevir/ritonavir ± ribavirin • sofosbuvir/velpatasvir • elbasvir/grazoprevir ± ribavirin • placebo or no treatment **Genotype 5:** • ledipasvir/sofosbuvir • sofosbuvir/velpatasvir • placebo or no treatment **Genotype 6:** • ledipasvir/sofosbuvir • sofosbuvir/velpatasvir • placebo or no treatment
Outcomes	**Key efficacy outcomes:** • sustained virologic response[e] • treatment failure • virologic failure (i.e., on-treatment failure or relapse) • health-related quality of life (HRQoL)[f] • patient-reported symptoms (e.g., fatigue)[f] • mortality (all-cause and liver-related)[f] **Other efficacy outcomes:** • hepatic-related morbidity outcomes (e.g., histological changes, hepatocellular carcinoma, liver failure, liver transplant) • work productivity **Harms outcomes:** • AEs, SAEs, WDAEs • harms of special interest: nausea, fatigue, anemia, pruritus, headache, ALT elevations, elevated bilirubin
Study Design	Published and unpublished phase III randomized controlled trials

AE = adverse event; ALT = alanine aminotransferase; CHC = chronic hepatitis C; DAA = direct-acting antiviral; HCV = hepatitis C virus; HRQoL = health-related quality of life; NS = nonstructural viral protein; PR = pegylated interferon plus ribavirin; RNA = ribonucleic acid; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] According to dosage regimens in draft product monograph.

[b] Experienced with PR, sofosbuvir + PR, sofosbuvir + ribavirin, simeprevir + sofosbuvir, simeprevir + PR, telaprevir + PR, or boceprevir + PR.

[c] Regimens containing ledipasvir, daclatasvir, or ombitasvir.

[d] Health Canada–approved dosage regimens.

[e] With ribavirin in liver-transplant patients.

[f] Outcomes identified as important, based on patient input.

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

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

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

The initial search was completed on July 7, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on November 15, 2017. 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/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Drug Class Reviews, Databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

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

Results

Findings from the Literature

A total of 10 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

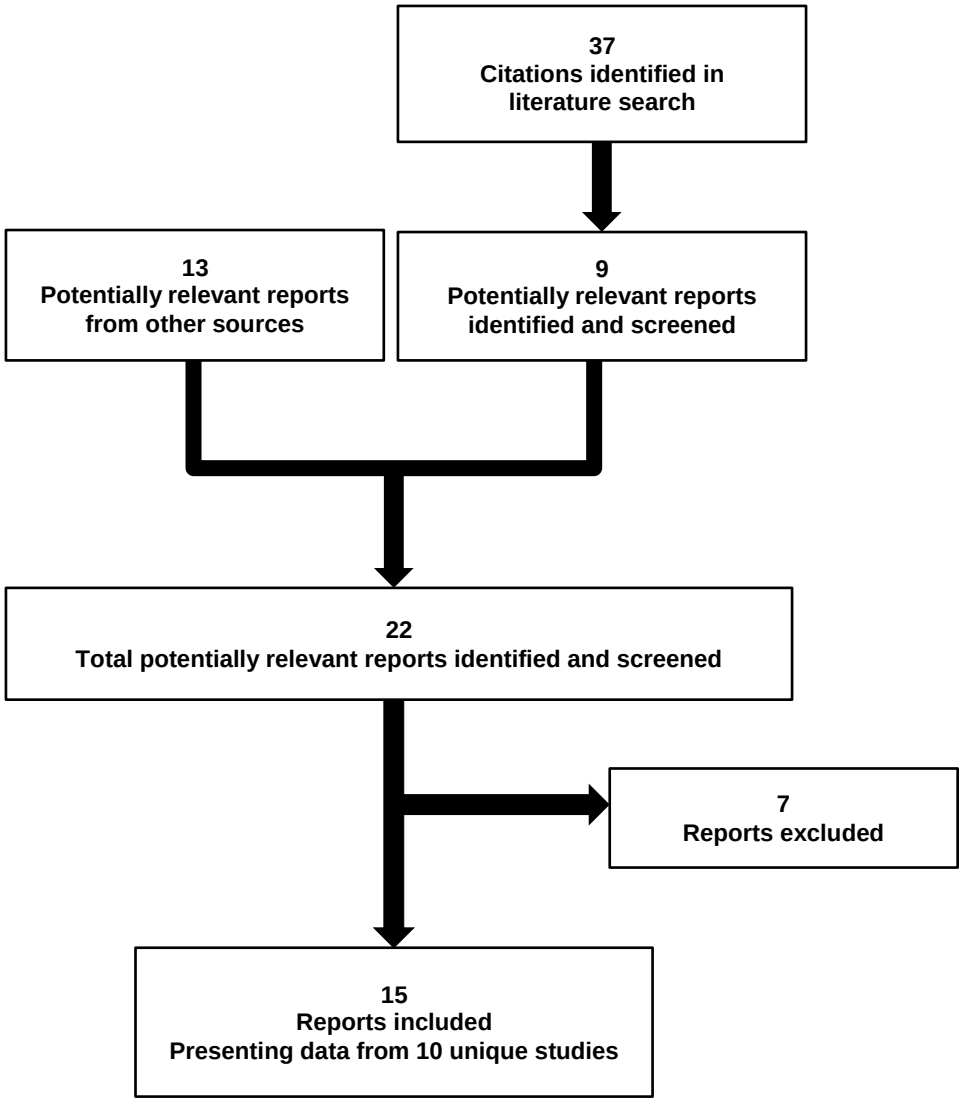


Table 5: Details of Included Studies

		ENDURANCE-1	ENDURANCE-2	ENDURANCE-3	CERTAIN-2
Designs and Populations	**Study Design**	OL phase III randomized trial (noninferiority versus historic control)	DB placebo-controlled, phase III RCT (noninferiority versus historic control)	OL, active-controlled, phase III RCT (noninferiority)	OL, active-controlled, phase III RCT (noninferiority)
	Locations	Canada, US, Europe, Asia, South America, Australia, and New Zealand	Europe, Asia, and US	Canada, US, Europe, Australia, and New Zealand	Japan (multi-centre)
	Randomized/ Enrolled (N)	704 (703 treated)	304 (302 treated)	506 (505 treated)	136
	Inclusion Criteria	• CHC genotype 1, with or without coinfection of HIV • TN or TE (IFN-based or SOF/RBV-based)[a] • Without cirrhosis • For patients with HIV coinfection: naive to any ART regimen or on stable, qualifying HIV-1 ART regimen for ≥ 8 weeks prior to screening	• CHC genotype 2 • TN or TE (IFN-based or SOF/RBV-based)[a] • Without cirrhosis	• CHC genotype 3 • TN • Without cirrhosis	• CHC genotype 2 • DAA-naive • Without cirrhosis • Females without childbearing potential or males/females using effective methods of birth control
	Exclusion Criteria	• HBsAg (+) • Infection with more than 1 HCV genotype • Other liver diseases • Drug or alcohol abuse within 6 months of randomization[b] • Failed previous regimen containing HCV PIs and/or NS5A inhibitors	• HBsAg (+) • Anti-HIV antibody (+) • Infection with more than 1 HCV genotype • Other liver diseases • Drug or alcohol abuse within 6 months of randomization[b]	• Previous use of any anti-HCV therapy • HBsAg (+) • Anti-HIV antibody (+) • Infection with more than 1 HCV genotype • Other liver diseases • Drug or alcohol abuse within 6 months of randomization[b]	• HBsAg (+) • Anti-HIV antibody (+) • Infection with more than 1 HCV genotype • Other liver diseases • Drug or alcohol abuse within 6 months of randomization[b] • History of solid-organ transplantation
Drugs	**Intervention**	Glecaprevir 300 mg / pibrentasvir 120 mg q.d. for 8 weeks Glecaprevir 300 mg / pibrentasvir 120 mg q.d. for 12 weeks	Glecaprevir 300 mg / pibrentasvir 120 mg q.d. for 12 weeks	Glecaprevir 300 mg / pibrentasvir 120 mg q.d. for 8 weeks Glecaprevir 300 mg / pibrentasvir 120 mg q.d. for 12 weeks	Glecaprevir 300 mg / pibrentasvir 120 mg q.d. for 8 weeks
	Comparator(s)	Historical control (used for noninferiority evaluation)	Matching placebo (following by OL glecaprevir 300 mg / pibrentasvir 120 mg q.d. for 12 weeks) Historical control (noninferiority evaluation)	SOF 400 mg / DCV 60 mg q.d. for 12 weeks	SOF + RBV for 12 weeks

		ENDURANCE-1	ENDURANCE-2	ENDURANCE-3	CERTAIN-2
Duration	**Phase**				
	Double-blind	–	12 weeks	–	–
	Open-label	8 or 12 weeks	12 weeks for patients originally in the PBO group	8 or 12 weeks	8 or 12 weeks
	Follow-up	24 weeks	24 weeks	24 weeks	24 weeks
Outcomes	**Primary End Point**	SVR 12 (mono-infected DAA-naive patients only)	SVR 12 (treatment-naive and prior IFN-based therapy patients only)	SVR 12	SVR 12
	Secondary End Point	• SVR 12 in patients coinfected with HIV-1 and with prior SOF experience • On-treatment virologic failure • Relapse	• On-treatment virologic failure • Relapse • % of patients in the GP group with prior SOF + RBV ± peg-IFN failure with SVR 12	• On-treatment virologic failure • Relapse	• On-treatment virologic failure • Relapse
	Other End Points	• HCV RNA < LLOQ at each visit • SVR4 and SVR24 • Relapse after achieving SVR 12 • EQ-5D-3L • Safety	• HCV RNA < LLOQ at each visit • SVR4 and SVR24 • EQ-5D-3L • SF-36v2 • FSS • WPAI-HCV • Responder analysis for SF-36 and FSS • Safety	• HCV RNA < LLOQ at each visit • SVR4 • EQ-5D-3L • SF-36v2 • FSS • WPAI-HCV • Safety	• HCV RNA < LLOQ at each visit • SVR4 and SVR24 • EQ-5D-3L • FSS • Responder analysis for FSS • Safety
Notes	**Publications**	–	Asselah 2017[38]	–	Toyoda 2017[39]

Table 5: Details of Included Studies (Continued)

		ENDURANCE-4	EXPEDITION-1	EXPEDITION-4
Designs and Populations	**Study Design**	Uncontrolled, open-label phase III study	Uncontrolled, open-label phase III study	Uncontrolled, open-label phase III study
	Locations	Canada, Europe, South Africa	Canada, US, Europe, South Africa	Canada, Europe, US, Australia, New Zealand
	Randomized/ Enrolled (N)	121	146	104
	Inclusion Criteria	• CHC genotype 4, 5, or 6 • TN or TE (IFN-based or SOF/RBV-based)[a]) • Without cirrhosis	• CHC genotype 1, 2, 4, 5, or 6 • TN or TE (IFN-based or SOF/RBV-based)[a]) • Compensated cirrhosis (Child-Pugh score ≤ 6) and no history of Child-Pugh B or C class or had history of liver decompensation	• CHC genotype 1 to 6 • TN or TE (IFN-based or SOF/RBV-based)[a]) • With or without cirrhosis • Severe renal impairment or ESRD (eGFR < 30 mL/min/1.73 m^2 by MDRD method)
	Exclusion Criteria	• Failed prior PI or NS5A inhibitor therapy • History of drug or alcohol abuse with past 6 months[b] • Hepatitis B or HIV infection	• Failed prior PI, NS5A inhibitor or NS5B inhibitor • History of drug or alcohol abuse with past 6 months[b] • Hepatitis B or HIV infection	• Treatment-experienced genotype 3 • Failed prior PI or NS5A inhibitor therapy • History of drug or alcohol

		ENDURANCE-4	EXPEDITION-1	EXPEDITION-4
		• Infection with more than one HCV genotype • Other liver diseases	• Infection with more than one HCV genotype • Other liver diseases • ALT or AST > 10 ULN or CrCl < 50 mL/min • Prior transplant	abuse with past 6 months[b] • Hepatitis B or HIV infection • Infection with more than one HCV genotype • Other liver diseases • Prior transplant or planned renal transplant
DRUGS	**Intervention**	Glecaprevir 300 mg / pibrentasvir 120 mg daily for 12 weeks	Glecaprevir 300 mg / pibrentasvir 120 mg daily for 12 weeks	Glecaprevir 300 mg / pibrentasvir 120 mg daily for 12 weeks
	Comparator(s)	None	None	None
DURATION	**Phase**			
	Double-blind			
	Open-label	12 weeks	12 weeks	12 weeks
	Follow-up	24 weeks	24 weeks	24 weeks
OUTCOMES	**Primary End Point**	SVR 12	SVR 12	SVR 12
	Secondary End Point	• On-treatment virologic failure • Relapse	• On-treatment virologic failure • Relapse	• On-treatment virologic failure • Relapse
	Other End Points	• HCV RNA < LLOQ at each visit • SVR4 and SVR24 • relapse after achieving SVR 12 • SF-36 (version 2) • FSS • EQ-5D 3L • WPAI-HCV • responder analysis (SF-36, FSS)	• HCV RNA < LLOQ at each visit • SVR4 and SVR24 • relapse after achieving SVR 12 • SF-36v2 • FSS • EQ-5D 3L • WPAI-HCV • responder analysis (SF-36, FSS)	• HCV RNA < LLOQ at each visit • SVR4 and SVR24 • relapse after achieving SVR 12 • SF-36v2 • FSS • EQ-5D 3L • responder analysis (SF-36, FSS)
NOTES	**Publications**	Asselah 2017[38]	Forns 2017[40]	Gane 2017[41]

Table 5: Details of Included Studies (Continued)

		MAGELLAN-1 Part 2	SURVEYOR-2 Part 3	SURVEYOR-2 Part 4
DESIGNS & POPULATIONS	**Study Design**	Prospective, randomized OL phase II clinical trial	Prospective. OL phase II clinical trial	Prospective, OL phase II clinical trial (noninferiority versus historical control)
	Locations	US, Europe, Australia, Puerto Rico	Australia, Canada, France, Korea, New Zealand, Taiwan, UK and US.	Australia, Canada, France, Korea, New Zealand, Taiwan, UK and US.
	Randomized/ Enrolled (N)	91	132 (131treated)	203
	Inclusion Criteria	• CHC genotype 1, 4, 5, or 6 • NS5A inhibitor (± PI)–experienced (limited to DCV, LDV, or OBV) or NS5A inhibitor–naive / NS3/4A PI–experienced (limited to PTV/r, SIM, TEL, and BOC regimens) • NS5A inhibitor–naive / NS3/4A PI–experienced (limited to PTV/r, SIM, TEL, and BOC regimens) • Compensated liver disease with or without cirrhosis	• CHC genotype 3 • TN with or without cirrhosis, or • TE (prior IFN or peg-IFN with or without RBV, or SOF + RBV) without cirrhosis	• CHC genotype 2, 4, 5, or 6 • TN or TE (prior IFN or peg-IFN with or without RBV or SOF + RBV) without cirrhosis

		MAGELLAN-1 Part 2	SURVEYOR-2 Part 3	SURVEYOR-2 Part 4
	Exclusion Criteria	• History of drug or alcohol abuse within past 6 months[b] • Hepatitis B or HIV infection • Infection with more than one HCV genotype • Other liver diseases • Patients enrolled with cirrhosis were excluded if they had a history of Child-Pugh (B or C class) or a history of liver decompensation	• Failed prior DAA (except for SOF) • History of drug or alcohol abuse with past 6 months[b] • Hepatitis B or HIV infection • Infection with more than one HCV genotype • Other liver diseases • Patients enrolled with cirrhosis were excluded if they had history of Child-Pugh B or C class or had history of liver decompensation	• Failed prior DAA (except for SOF) • History of drug or alcohol abuse with past 6 months[b] • Hepatitis B or HIV infection • Infection with more than one HCV genotype • Other liver diseases
DRUGS	**Intervention**	Glecaprevir 300 mg / pibrentasvir 120 mg daily for 12 weeks or 16 weeks	Glecaprevir 300 mg / pibrentasvir 120 mg daily as follows: • TN with cirrhosis (12 weeks) • TE with cirrhosis (16 weeks) • TE without cirrhosis randomized to 12 or 16 weeks	Glecaprevir 300 mg / pibrentasvir 120 mg daily for 8 weeks
	Comparator(s)	None	None	Historical control for genotype 2 patient group No control for genotype 4,5, 6, group
DURATION	**Phase**			
	Double-blind	–	–	–
	Open-label	12 or 6 weeks	12 or 16 weeks	8 weeks
	Follow-up	24 weeks	24 weeks	24 weeks
OUTCOMES	**Primary End Point**	SVR 12	SVR 12	SVR 12
	Secondary End Point	• SVR4 • On-treatment virologic failure • Relapse	• SVR4 • On-treatment virologic failure • Relapse	• SVR4 • On-treatment virologic failure • Relapse
	Other End Points	• HCV RNA < LLOQ at each visit • SVR24 • Relapse after achieving SVR 12	• HCV RNA < LLOQ at each visit • SVR24 • Relapse after achieving SVR 12 • SF-36v2 • FSS • EQ-5D 5L • WPAI-HCV	• HCV RNA < LLOQ at each visit • SVR24 • Relapse after achieving SVR 12 • SF-36v2 • FSS • EQ-5D 5L • WPAI-HCV
NOTES	**Publications**	–	Wyles 2017[42]	Asselah 2017[38]

ALT = alanine aminotransferase; ART = antiretroviral treatment; AST = aspartate aminotransferase; BOC = boceprevir; CDR = CADTH Common Drug Review; CHC = chronic hepatitis C; CrCl = creatinine clearance; DAA = direct-acting antiviral; DB = double-blind; DCV = daclatasvir; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FSS = Fatigue Severity Scale; GP = glecaprevir/pibrentasvir; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus-1; IFN = interferon; LDV = ledipasvir; LLOQ = lower limit of quantitation; min = minute; MDRD = Modification of Diet in Renal Disease; NS = nonstructural viral protein; OBV = ombitasvir; OL = open-label; PBO = placebo; peg-IFN = pegylated interferon; PI = protease inhibitor; PRO = patient-reported outcome; PTV/r = paritaprevir/ritonavir; q.d. = once daily; RBV = ribavirin; RCT = randomized controlled trial; RNA = ribonucleic acid; SF-36v2 = Short Form (36) Health Survey, version 2; SIM = simeprevir; SOF = sofosbuvir; SVR4, 12, or 24 = sustained virologic response 4, 12, or 24 weeks after end of treatment; TE = treatment-experienced; TEL = telaprevir; TN = treatment-naive; ULN = upper limit of normal; WPAI-HCV = Work Productivity and Activity Impairment – Hepatitis C.

[a] IFN-based prior treatment included IFN or peg-IFN with or without RBV; SOF/RBV-based prior treatment included SOF plus RBV, with or without peg-IFN.

[b] If the drug or alcohol use could preclude adherence to the protocol in the opinion of the investigator.

Note: One additional report was included (CDR submission[43]).

Source: Clinical Study Reports.[6,11-18]

Included Studies

Description of Studies

A total of nine reports presenting data from 10 unique studies were included in the review. Some reports contained data on multiple studies (e.g., MAGELLAN-1, SURVEYOR-II); however, only those parts that met the inclusion criteria were summarized.

Three trials were open-label single-group studies (EXPEDITION-1, EXPEDITION-4, ENDURANCE-4) and four trials were open-label studies that randomized or assigned patients to more than one GP treatment group (ENDURANCE-1, SURVEYOR-II Part 3 and Part 4, MAGELLAN-1 Part 2). Two trials were open-label randomized controlled noninferiority trials (CERTAIN-2, ENDURANCE-3, and one trial was a randomized double-blind study (ENDURANCE-2).

Patients who entered the non-randomized or randomized studies were enrolled using an interactive response technology system. In the randomized studies, computer-generated randomization numbers were assigned by the manufacturer before the start of the trial. Three trials (ENDURANCE-1, ENDURANCE-2, SURVEYOR-II Part 4) compared the rate of sustained virologic response at 12 weeks (SVR 12) of patients on GP with a historical control to determine noninferiority.

In the ENDURANCE-1 study, eligible genotype 1 CHC patients were randomized 1:1 to either 8 or 12 weeks of GP, stratified by HCV RNA viral load (< or ≥ 6 million IU/mL) and by genotype subtype (1b or non-1b). Noninferiority of GP for 12 weeks versus a historical control (ombitasvir/paritaprevir/ritonavir plus dasabuvir ± ribavirin or sofosbuvir/ledipasvir for 12 weeks; SVR 12 rate: 97%) was met if the lower limit of the 95% confidence interval (CI) for the SVR 12 rate was greater than 91% (i.e., 6% noninferiority margin).

The ENDURANCE-2 study randomized genotype 2 CHC patients to GP or placebo (1:1) for the first 12 weeks (double-blind period) to evaluate safety. After 12 weeks, patients in the placebo group received open-label GP for 12 weeks. Randomization was stratified by previous treatment experience (treatment-naive, prior IFN-based, or prior sofosbuvir/ribavirin-based therapy). Patients who had received prior sofosbuvir/ribavirin ± peg-IFN treatment were analyzed separately. Patients and investigators were blinded to treatment allocation during the first 12 weeks, and any laboratory data that could potentially unblind patients data was assessed by an independent reviewer. The SVR 12 rate for the GP 12-week group was compared with a historical control (sofosbuvir/ribavirin; SVR 12 rate: 95%) and GP for 12 weeks was deemed noninferior if the lower limit of the 95% CI was greater than 89%.

ENDURANCE-3 was designed to demonstrate the noninferiority of 12 weeks of GP to 12 weeks of sofosbuvir/daclatasvir (daclatasvir). Patients with genotype 3 HCV infection were randomized 2:1 to GP or sofosbuvir 400 mg plus daclatasvir 60 mg daily for 12 weeks. A third treatment group (GP for 8 weeks) was available for enrolment after the other two treatment groups were complete. GP for 12 weeks was deemed noninferior to sofosbuvir/daclatasvir if the lower bound of the 95% CI was above the −6% noninferiority margin or was greater than 92%.

In the CERTAIN-2 trial, patients with genotype 2 HCV infection were randomized 2:1 to GP for 8 weeks or sofosbuvir 400 mg plus ribavirin 600 mg to 1,000 mg (weight-based) daily for 12 weeks. Randomization was stratified by prior treatment experience (treatment-

naive or prior IFN-based therapy) and HCV RNA viral load (< or ≥ 6 million IU/mL). GP for 8 weeks was deemed noninferior to sofosbuvir/ribavirin if the lower bound of the 95% CI was above the −10% noninferiority margin.

In the SURVEYOR-II Part 3 study, genotype 3 patients who were treatment-experienced and without cirrhosis were randomized 1:1 to either 12 or 16 weeks of GP. Those with genotype 3 HCV infection and cirrhosis who were treatment-naive were enrolled in a 12-week GP group and those who were treatment-experienced received 16 weeks of GP. In SURVEYOR-II Part 4, all patients received 8 weeks of GP, but those with genotype 2 HCV infection were analyzed separately from those with genotype 4, 5, or 6. For genotype 2 patients, GP for 8 weeks was considered noninferior to the historical control (sofosbuvir/ribavirin for 12 weeks; SVR 12 rate: 95%) if the lower limit of the 95% CI was greater than 89%.

In MAGELLAN-1 Part 2, eligible patients were randomized to receive either 12 or 16 weeks of GP. Randomization was stratified by genotype (1 versus 4 to 6) and by prior DAA regimen (NS5A-experienced or PI-experienced/NS5A-naive). All patients in the single-group studies (EXPEDITION-1, EXPEDITION-4, ENDURANCE-4) received GP for 12 weeks and were evaluated for viral response.

Populations

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria of the trials varied in terms of the patients' genotype, treatment history, and presence of cirrhosis (Table 6). All trials excluded patients with hepatitis B, and all but one (ENDURANCE-1) excluded those with HIV coinfection. Only one trial enrolled patients who had failed a DAA-based treatment (MAGELLAN-1 Part 2). In this phase II study, the patients enrolled had an inadequate response to an NS5A inhibitor (limited to daclatasvir, ledipasvir, or ombitasvir) or an NS3/4A inhibitor (paritaprevir/ritonavir, simeprevir, telaprevir, or boceprevir regimens). In other studies, treatment-experienced patients had failed to respond to either IFN or peg-IFN with or without ribavirin (i.e., IFN-based), or sofosbuvir plus ribavirin with or without peg-IFN (i.e., sofosbuvir/ribavirin-based). The EXPEDITION-4 study enrolled patients with end-stage renal disease (ESRD), including those receiving dialysis. All trials enrolled patients from multiple countries, except for CERTAIN-2, which only included patients from Japan.

Table 6: Summary of Populations Eligible for Enrolment

Study	Population	Treatment-Naive	Treatment-Experienced	Cirrhosis
ENDURANCE-1	Genotype 1 (including HIV coinfected)	Included	IFN-based or SOF/RBV-based[a]	Excluded
ENDURANCE-2	Genotype 2	Included	IFN-based or SOF/RBV-based[a]	Excluded
ENDURANCE-3	Genotype 3	Included	excluded	Excluded
ENDURANCE-4	Genotype 4, 5, or 6	Included	IFN-based or SOF/RBV-based[a]	Excluded
CERTAIN-2	Genotype 2 (Japan)	Included	IFN-based[a]	Excluded
SURVEYOR-II Part 3	Genotype 3	Included	IFN-based or SOF/RBV-based[a]	No cirrhosis or compensated cirrhosis
SURVEYOR-II Part 4	Genotype 2, 4, 5, or 6	Included	IFN-based or SOF/RBV-based[a]	Excluded

Study	Population	Treatment-Naive	Treatment-Experienced	Cirrhosis
EXPEDITION-1	Genotype 1, 2, 4, 5, or 6	Included	IFN-based or SOF/RBV-based[a]	Compensated cirrhosis
EXPEDITION-4	• Genotype 1 to 6 • Severe renal impairment or ESRD (including those on dialysis)	Included	IFN-based or SOF/RBV-based[a]	With or without cirrhosis
MAGELLAN-1 Part 2	Genotype 1, 4, 5, or 6[b]	Excluded	• NS5A inhibitor (± PI)–experienced (limited to DCV, LDV, or OBV) or • NS5A inhibitor–naive / NS3/4A PI–experienced (limited to PTV/r, SIM, TEL, and BOC regimens)	No cirrhosis or compensated cirrhosis

BOC = boceprevir; DCV = daclatasvir; ESRD = end-stage renal disease; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PI = protease inhibitor; PTV/r = paritaprevir/ritonavir; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir.
[a] IFN-based prior treatment that included IFN or peg-IFN with or without RBV, and SOF/RBV-based treatment that included SOF plus RBV with or without peg-IFN.
[b] Although patients with genotype 5 or 6 HCV infection were eligible for enrolment, none of these patients were included in MAGELLAN-1 Part 2.
Source: Clinical Study Reports.[6,11-18]

Baseline Characteristics

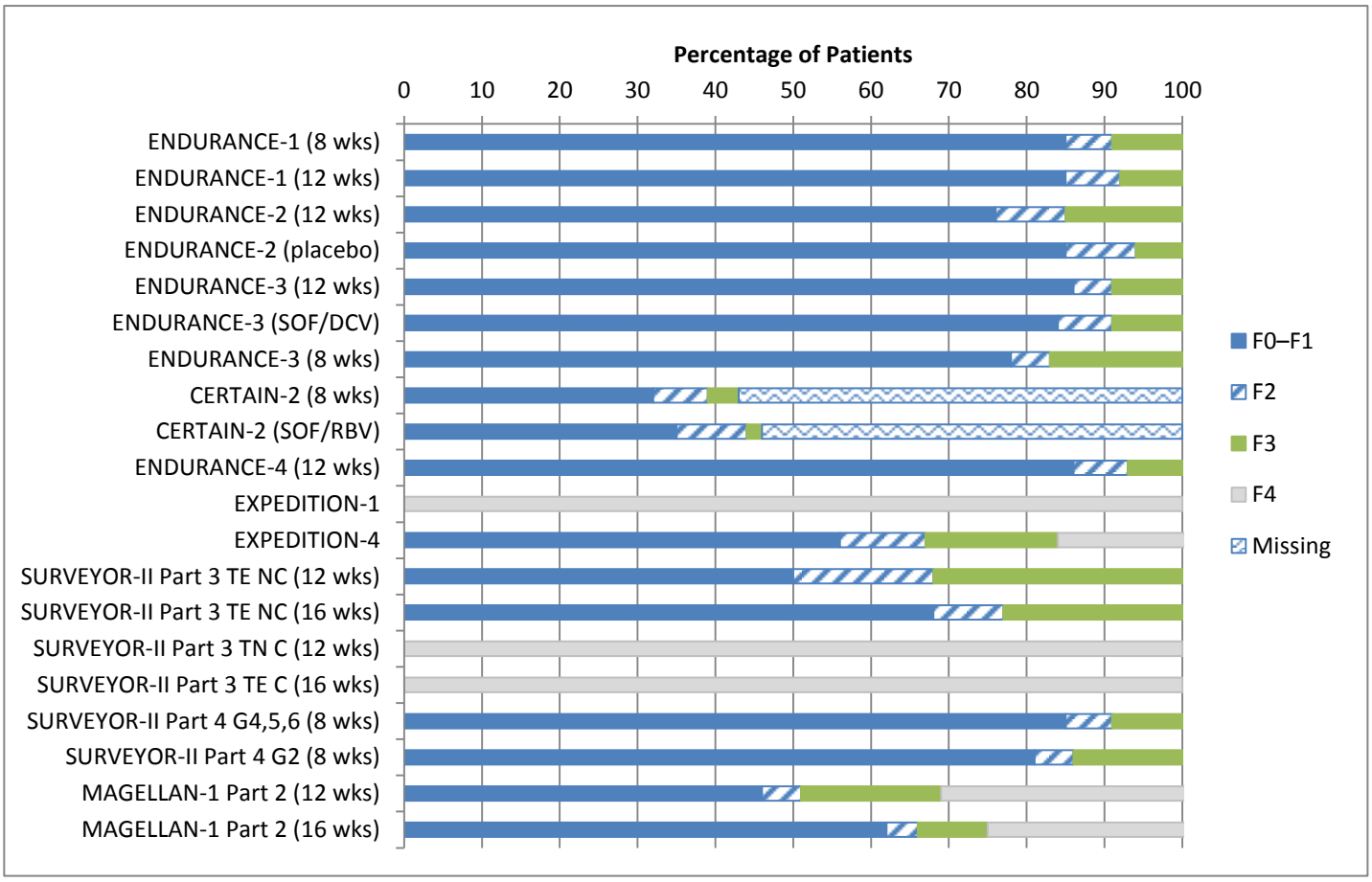
The trials enrolled patients with a mean age per treatment group that ranged from 45.4 years to 60.1 years and who were predominantly white (60% to 93%; except CERTAIN-2, in which all patients were Japanese) (Table 7). The majority of patients in most treatment groups were fibrosis stage F0 or F1 at baseline. Overall, relatively few patients had cirrhosis and, except for EXPEDITION-1, EXPEDITION-4, SURVEYOR-II Part 3, and MAGELLAN-1 Part 2, less than 20% of patients had fibrosis levels F3 or F4 (Figure 2).

In the EXPEDITION-4 study, most patients were receiving dialysis (N = 85, 82%), and among those not requiring dialysis, 13 patients (13%) had stage 4 chronic kidney disease and six (6%) had stage 5 disease.

In the MAGELLAN study, 32% and 28% had prior NS3/4A protease inhibitor therapy and 36% and 38% had prior NS5A inhibitor treatment, and 32% and 34% had received both classes of treatment in the 12-week and 16-week groups, respectively (Table 7). Among other trials that included treatment-experienced patients, more patients had received IFN-based therapy than sofosbuvir/ribavirin-based treatment.

The patient characteristics appeared to be balanced between groups in the three trials with a comparator group (ENDURANCE-2, ENDURANCE-3, and CERTAIN-2).

Figure 2: Fibrosis Stage of Enrolled Patients



C = cirrhosis; DCV = daclatasvir; G = genotype; NC = no cirrhosis; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive; wks = weeks.
Source: Clinical Study Reportss.[6,11-18]

Table 7: Summary of Baseline Characteristics (Safety Population)

	ENDURANCE-1		ENDURANCE-2		ENDURANCE-3			CERTAIN-2	
Treatment Group	**GP 8 Weeks**	**GP 12 Weeks**	**GP 12 Weeks**	**PBO**	**GP 12 Weeks**	**SOF + DCV 12 Weeks**	**GP 8 Weeks**	**GP 8 Weeks**	**SOF + RBV 12 Weeks**
Population	**G 1 TN, TE No Cirrhosis**		**G 2 TN, TE No Cirrhosis**		**G 3 TN, No Cirrhosis**			**G 2 DAA-Naive, No Cirrhosis**	
Total N	**351**	**352**	**202**	**100**	**233**	**115**	**157**	**90**	**46**
Age, mean (SD)	52.0 (11.9)	50.0 (11.6)	56.8 (12.8)	57.6 (12.0)	47.2 (10.7)	47.1 (11.3)	45.4 (12.2)	57.5 (13.1)	58.9 (13.6)
Male, n (%)	167 (48)	176 (50)	98 (48.5)	45 (45.0)	121 (51.9)	52 (45.2)	92 (58.6)	42 (46.7)	21 (45.7)
Race, n (%)									
White	289 (82)	302 (86)	121 (59.9)	60 (60.0)	205 (88.0)	103 (89.6)	134 (85.4)	–	–

	ENDURANCE-1		ENDURANCE-2		ENDURANCE-3			CERTAIN-2	
Treatment Group	**GP 8 Weeks**	**GP 12 Weeks**	**GP 12 Weeks**	**PBO**	**GP 12 Weeks**	**SOF + DCV 12 Weeks**	**GP 8 Weeks**	**GP 8 Weeks**	**SOF + RBV 12 Weeks**
Black or African American	14 (4)	12 (3)	7 (3.5)	7 (7.0)	3 (1.3)	3 (2.6)	3 (1.9)	–	–
Asian	44 (13)	34 (10)	69 (34.2)	32 (32.0)	19 (8.2)	4 (3.5)	13 (8.3)	90 (100)	46 (100)
Other	4 (1)	4 (1)	5 (2.5)	1 (1.0)	6 (2.6)	5 (4.4)	7 (4.4)	–	–
HCV genotype, n (%)									
G 1	351 (100)	352 (100)	–	–	–	–	–	–	–
G 2	–	–	202 (100)	100 (100)	–	–	–	90 (100)	46 (100)
G 3	–	–	–	–	233 (100)	115 (100)	157 (100)	–	–
G 4	–	–	–	–	–	–	–	–	–
G 5	–	–	–	–	–	–	–	–	–
G 6	–	–	–	–	–	–	–	–	–
Baseline HCV RNA									
Log_{10} IU/mL, mean (SD)	6.05 (0.73)	6.10 (0.59)	6.06 (0.87)	6.09 (0.82)	6.1 (0.8)	6.0 (0.7)	6.0 (0.9)	6.0 (0.81)	6.1 (0.79)
≥ 6,000,000 IU/mL, n (%)	49 (14)	43 (12)	47 (23.3)	18 (18.0)	65 (27.9)	14 (12.2)	34 (21.7)	8 (8.9)	6 (13.0)
Cirrhosis, n (%)	0	0	0	0	0	0	0	0	0
Fibrosis stage, n (%)									
F0−F1	296 (85)	298 (85)	154 (76.2)	85 (85.0)	201 (86.3)	97 (84.3)	122 (77.7)	29/39 (74.4) [a]	16/21 (76.2) [a]
F2	22 (6)	24 (7)	18 (8.9)	9 (9.0)	12 (5.2)	8 (7.0)	8 (5.1)	6/39 (15.4) [a]	4/21 (19.0) [a]
F3	30 (9)	29 (8)	30 (14.9)	6 (6.0)	20 (8.6)	10 (8.7)	27 (17.2)	4/39 (10.3) [a]	1/21 (4.8) [a]
F4	0	0	0	0	0	0	0	NR	NR
Treatment history, n (%)									
TN	219 (62)	217 (62)	141 (69.8)	71 (71.0)	233 (100)	115 (100)	157 (100)	75 (83.3)	38 (82.6)
TE	132 (38)	135 (38)	61 (30.2)	29 (29.0)	0	0	0	15 (16.7)	8 (17.4)
Prior HCV therapy, n/N (%)									
Other DAA	NR	NR	NR	NR	No prior HCV therapy			Excluded	Excluded
SOF/RBV-based	1 (0.3)	2 (0.6)	6 (3.0)	2 (2.0)				Excluded	Excluded
IFN-based	131 (37)	133 (38)	55 (27.2)	27 (27.0)				15 (16.7)	8 (17.4)
Other									
Prior treatment response, n/N (%)									
On-treatment nonresponder/ breakthrough	61 (17)	55 (16)	11 (5.4)	5 (5.0)	No prior HCV therapy			1 (1.1)	0
Relapse	45 (13)	71 (20)	36 (17.8)	15 (15.0)				9 (10.0)	7 (15.2)
Unknown/other	26 (7)	9 (3)	14 (6.9)	9 (9.0)				5 (5.5)	1 (2.2)
Baseline eGFR (mL/min/1.73m^2)									
Mean (SD)	90.9 (17.5)	92.8 (18.5)	91.63 (16.49)	90.58 (16.92)	93.42 (16.62)	92.02 (18.92)	95.21 (17.65)	77.3 (16.06)	78.1 (14.88)
Range	44.3–188.1	49.1–162.3	55.3–138.9	55.4–140.4	47.7–151.6	50.7–163.9	58.0–143.8	51.0–131.9	50.4–118.4

	ENDURANCE-1		ENDURANCE-2		ENDURANCE-3			CERTAIN-2	
Treatment Group	**GP 8 Weeks**	**GP 12 Weeks**	**GP 12 Weeks**	**PBO**	**GP 12 Weeks**	**SOF + DCV 12 Weeks**	**GP 8 Weeks**	**GP 8 Weeks**	**SOF + RBV 12 Weeks**
HIV coinfection, n (%)	15 (4)[b]	18 (5)[b]	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded

Table 7: Summary of Baseline Characteristics (Safety Population) (Continued)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4
Treatment Group	**GP 12 Weeks**	**GP 12 Weeks**	**GP 12 Weeks**
Population	**G 4, 5, 6 TN, TE No Cirrhosis**	**G 1, 2, 4, 5, 6 TN, TE Cirrhosis**	**G 1–6 Renal Impairment TN, TE With/Without Cirrhosis**
Total N	**121**	**146**	**104**
Age, mean (SD)	52.7 (11.0)	60.1 (10.4)	57.5 (11.1)
Male, n (%)	77 (64)	90 (62)	79 (76)
Race, n (%)			
White	84 (71)	120 (82)	64 (62)
Black or African American	8 (7)	15 (10)	25 (24)
Asian	24 (20)	10 (7)	9 (9)
Other	2 (2)	1 (1)	6 (6)
HCV genotype, n (%)			
G 1	–	87 (60)	54 (52)
G 2	–	34 (23)	17 (16)
G 3	–	–	11 (11)
G 4	76 (63)	16 (11)	20 (19)
G 5	26 (22)	2 (1)	1 (1)
G 6	19 (16)	7 (5)	1 (1)
Baseline HCV RNA			
Log_{10} IU/mL, mean (SD)	6.1 (0.66)	6.1 (0.69)	5.9 (0.7)
≥ 6,000,000 IU/mL, n (%)	22 (18)	17 (12)	8 (8)
Cirrhosis, n (%)	Excluded	146 (100)	20 (19)
Fibrosis stage, n (%)			
F0−F1	104 (86)	NR[c]	58 (56)
F2	8 (7)		11 (11)
F3	9 (7)		17 (17)
F4	0		17 (17)
Treatment history, n (%)			
TN	82 (68)	110 (75)	60 (58)
TE	39 (32)	36 (25)	44 (42)
Prior HCV therapy, n/N (%)			
Other DAA	NA	NA	NA
SOF/RBV-based	0	11 (8)	2 (2)
IFN-based	39 (32)	25 (17)	42 (40)
Other	0	0	0
Prior treatment response, n/N (%)			

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4
Treatment Group	**GP 12 Weeks**	**GP 12 Weeks**	**GP 12 Weeks**
Nonresponder/breakthrough	15 (12)	11 (8)	17 (16)
Relapse	18 (15)	15 (10)	13 (13)
Unknown/other	6 (5)	10 (7)	14 (14)
Baseline eGFR (mL/min/1.73m^2)			
Mean (SD)	98.2 (21.7)	93.3 (21.9)	10.6 (6.4)
Range	54.1, 204.3	43.5, 166.9	3.8, 41.2
HIV coinfection, n (%)	Excluded	Excluded	Excluded

Table 7: Summary of Baseline Characteristics (Safety Population) (Continued)

	SURVEYOR-II Part 3				SURVEYOR-II Part 4	
Treatment Group	**GP 12 Weeks**	**GP 16 Weeks**	**GP 12 Weeks**	**GP 16 Weeks**	**GP 8 Weeks**	**GP 8 Weeks**
Population	**G 3 TE No Cirrhosis**	**G 3 TE No Cirrhosis**	**G 3 TN Cirrhosis**	**G 3 TE Cirrhosis**	**G 2 TN, TE No Cirrhosis**	**G 4, 5, 6 TN, TE No Cirrhosis**
Total N	**22**	**22**	**40**	**47**	**145**	**58**
Age, mean (SD)	56.6 (7.4)	56.6 (8.9)	54.6 (7.8)	58.7 (5.8)	53.5 (11.8)	48.4 (13.8)
Male, n (%)	14 (64)	14 (64)	24 (60)	36 (77)	61 (42)	37 (64)
Race, n (%)						
White	17 (77)	20 (91)	37 (93)	42 (89)	120 (83)	35 (60)
Black or African American	0		0	0	11 (8)	10 (17)
Asian	5 (23)	2 (9)	1 (3)	3 (6)	10 (7)	13 (22)
Other	0	0	0	2 (4)	4 (3)	0
HCV genotype, n (%)						
G 1						
G 2					145 (100)	
G 3	22 (100)	22 (100)	40 (100)	47 (100)		
G 4						46 (79)
G 5						2 (3)
G 6						10 (17)
Baseline HCV RNA						
Log_{10} IU/mL, mean (SD)	6.4 (0.8)	6.2 (0.8)	6.1 (0.6)	6.3 (0.6)	6.3 (1.0)	5.7 (0.9)
≥ 6,000,000 IU/mL, n (%)	9 (41)	7 (32)	4 (10)	10 (21)	62 (43)	9 (16)
Cirrhosis, n (%)	0	0	40 (100)	47 (100)	Excluded	Excluded
Fibrosis stage, n (%)						
F0−F1	11 (50)	15 (68)	0	0	123 (85)	47 (81)
F2	4 (18)	2 (9)	0	0	9 (6)	3 (5)
F3	7 (32)	5 (23)	0	0	13 (9)	8 (14)
F4	0	0	40 (100)	47 (100)	0	0
Treatment history, n (%)						
TN	0	0	40 (100)	0	127 (88)	49 (85)
TE	22 (100)	22 (100)	0	47 (100)	18 (12)	9 (16)
Prior HCV therapy, n/N (%)						
Other DAA						
SOF/RBV-based	8 (36)	9 (41)	0	25 (53)	6 (4)	0
IFN-based	14 (64)	13 (59)	0	22 (47)	12 (8)	9 (16)
Other						

	SURVEYOR-II Part 3				SURVEYOR-II Part 4	
Treatment Group	**GP 12 Weeks**	**GP 16 Weeks**	**GP 12 Weeks**	**GP 16 Weeks**	**GP 8 Weeks**	**GP 8 Weeks**
Prior treatment response, n/N (%)						
Nonresponder/breakthrough	2 (9)	3 (14)	0	12 (26)	2 (1)	4 (7)
Relapse	17 (77)	19 (86)	0	33 (70)	14 (10)	3 (5)
Unknown/other	3 (14)	0	0	2 (4)	2 (1)	2 (3)
NA		0	0	0		
Baseline eGFR (mL/min/1.73m^2)						
Mean (SD)	95.0 (18.8)	86.1 (18.2)	94.8 (19.8)	93.3 (18.0)	89.7 (17.7)	99.9 (25.0)
Range	71.8, 140.4	56.6, 133.3	38.4, 150.8	62.6, 137.9	50.3, 137.9	62.2, 176.8
HIV coinfection, n (%)	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded

Table 7: Summary of Baseline Characteristics (Safety Population) (Continued)

	MAGELLAN-1 Part 2	
Treatment Group	**GP 12 Weeks**	**GP 16 Weeks**
Population	**G 1 or 4, DAA-Experienced, With/Without Cirrhosis**	**G 1 or 4, DAA-Experienced, With/Without Cirrhosis**
Total N	**44**	**47**
Age, mean (SD)	55.6 (8.6)	55.6 (8.3)
Male, n (%)	31 (71)	33 (70)
Race, n (%)		
White	34 (77)	35 (75)
Black or African American	9 (21)	11 (23)
Asian	1 (2)	1 (2)
Other		
HCV genotype, n (%)		
G 1	43 (98)	44 (94)
G 2	NA	NA
G 3	NA	NA
G 4	1 (2)	3 (6)
G 5	0	0
G 6	0	0
Baseline HCV RNA		
Log_{10} IU/mL, mean (SD)	6.0 (0.66)	6.2 (0.56)
≥ 6,000,000 IU/mL, n (%)	4 (9)	9 (19)
Cirrhosis, n (%)	15 (34)	12 (26)
Fibrosis stage, n (%)		
F0−F1	20 (46)	29 (62)
F2	2 (5)	2 (4)
F3	8 (18)	4 (9)
F4	14 (32)	12 (26)
Treatment history, n (%)		
Treatment-naive	0	0
Treatment-experienced	44 (100)	47 (100)

	MAGELLAN-1 Part 2	
Treatment Group	**GP 12 Weeks**	**GP 16 Weeks**
Population	**G 1 or 4, DAA-Experienced, With/Without Cirrhosis**	**G 1 or 4, DAA-Experienced, With/Without Cirrhosis**
Total N	**44**	**47**
Prior HCV therapy, n/N (%)		
NS3/4A PI–experienced / NS5A-naive	14 (32)	13 (28)
NS5A-experienced / NS3/4A PI–experienced	14 (32)	16 (34)
NS5A-experienced / NS3/4A PI–naive	16 (36)	18 (38)
Prior treatment response, n/N (%)		
Nonresponder/breakthrough	14 (32)	13 (28)
Relapse	30 (68)	34 (72)
Unknown/other	0	0
Baseline CrCl (mL/min)		
Mean (SD)	118.5 (30.1)	126.7 (38.6)
Range	73.2, 199.0	50.0, 256.0
HIV coinfection, n (%)	Excluded	Excluded

ART = antiretroviral treatment; CrCl = creatinine clearance; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; G = genotype; GP = glecaprevir/pibrentasvir; HCV = hepatitis C virus; IFN = interferon; min = minute; NA = not applicable; NR = not reported; PBO = placebo; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RNA = ribonucleic acid; SD = standard deviation; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive.
[a] Based on non-missing data. Fibrosis stage was not available for 51 patients in the GP group and 25 patients in the SOF group.
[b] All patients with HIV were receiving ART.
[c] All patients enrolled had compensated cirrhosis (Child-Pugh score ≤ 6).
Source: Clinical Study Reports.[6,11-18]

Interventions

A summary of the treatment groups in the trials is listed in Table 8. The dose of GP administered was glecaprevir 300 mg and pibrentasvir 120 mg once daily for 8, 12, or 16 weeks. The treatment duration of GP in some trials was not consistent with the Health Canada–approved regimen. In Table 8, the areas shaded in grey indicate the approved treatment duration for that study's population. No patients in ENDURANCE-2 or -4, and < 38% in EXPEDITION-4 and MAGELLAN-1 Part 2, received the duration of GP recommended by Health Canada.

Three trials included a control treatment other than GP. The control group in CERTAIN-2 received sofosbuvir 400 mg plus ribavirin 600 mg to 1,000 mg (weight-based) daily for 12 weeks and, in ENDURANCE-3, control patients received sofosbuvir 400 mg plus DCV 60 mg daily for 12 weeks. In ENDURANCE-2, the control group received a matching placebo for the first 12 weeks for the evaluation of safety, and then was administered GP.

All trials were open-label except for the first 12 weeks of ENDURANCE-2. Patients who met the HCV virologic stopping criteria during treatment had their therapy discontinued. The stopping criteria were similar across trials and are defined in Appendix 4 (Table 14). During the double-blind period in ENDURANCE-2, an independent reviewer assessed all virologic data to maintain blinding. No virologic stopping criteria were applied to patients receiving placebo.

In the ENDURANCE-1 trial, patients coinfected with HIV were enrolled if they were not receiving antiretroviral therapy (ART) or if they were on a stable ART regimen that included one of the following: raltegravir, dolutegravir, or rilpivirine, combined with two of the following nucleoside/nucleotide reverse transcriptase inhibitors: tenofovir disoproxil fumarate, emtricitabine, lamivudine, abacavir, or zidovudine.

Table 8: Summary of Treatment Groups

Study	Treatment Group	Genotype	Cirrhosis	Treatment History	GP 8 Weeks (N)	GP 12 Weeks (N)	GP 16 Weeks (N)	Other Treatment (N)
ENDURANCE-1	GP	1 (incl HIV)	no	TN, IFN, SOF/RBV	351			
	GP	1 (incl HIV)	no	TN, IFN, SOF/RBV		352		
ENDURANCE-2 (RCT)	GP	2	no	TN, IFN, SOF/RBV		202		
	PBO/GP	2	no	TN, IFN, SOF/RBV		100		
ENDURANCE-3	GP	3	no	TN	115			
RCT	GP	3	no	TN		230		
	SOF/DCV	3	no	TN				115
ENDURANCE-4	GP	4, 5, 6	no	TN, IFN, SOF/RBV		121		
CERTAIN-2	GP	2	no	TN, IFN	90			
RCT	SOF/RBV	2	no	TN, IFN				46
SURVEYOR-II Part 3	GP	3	no	IFN, SOF/RBV		22		
	GP	3	no	IFN, SOF/RBV			22	
	GP	3	yes	TN		40		
	GP	3	yes	IFN, SOF/RBV			47	
SURVEYOR-II Part 4	GP	2	no	TN, IFN, SOF/RBV	145			
	GP	4, 5, 6	no	TN, IFN, SOF/RBV	58			
EXPEDITION-1	GP	1, 2, 4, 5, 6	yes	TN, IFN, SOF/RBV		146		
EXPEDITION-4	GP	1 to 6 (ESRD)	Yes/no	TN, IFN, SOF/RBV		104[a]		
MAGELLAN-1 Part 2	GP	1, 4[b]	Yes/no	NS5A or NS3/4A PI		44[c]		
	GP	1, 4[b]	Yes/no	NS5A or NS3/4A PI			47[d]	

DCV = daclatasvir; ESRD = end-stage renal disease; GP = glecaprevir/pibrentasvir; IFN = interferon; N = number of patients enrolled; NS = nonstructural viral protein; PBO = placebo; PI = protease inhibitor; RBF = ribavirin; RCT = randomized controlled trial; SOF = sofosbuvir; TN = treatment-naive.

[a] For treatment-naive or prior IFN- or SOF/RBV-based treatment-experienced patients, Health Canada recommends GP for 12 weeks for patients with cirrhosis and 8 weeks for those without cirrhosis, except for treatment-experienced patients with genotype 3 HCV infection, who should receive 16 weeks of GP. In EXPEDITION-4, 17% of patients had cirrhosis and received the treatment duration consistent with Health Canada recommendations. It is unknown how many of the 11 patients with genotype 3 HCV infection were treatment-experienced and, therefore, should have received 16 weeks of treatment.

[b] Although patients with genotype 5 and 6 were eligible for enrolment, none entered the trial. In total, 4% of patients had genotype 4 and 96% had genotype 1 HCV infection.

[c] GP 12-week duration consistent with Health Canada recommendation for genotype 1 patients with or without cirrhosis who were NS5A inhibitor–naive. Approximately 32% of patients in the GP 12-week group were NS5A inhibitor–naive.

[d] GP 16-week duration is consistent with Health Canada recommendation for genotype 1 patients with or without cirrhosis who are NS5A-experienced and NS3/4A inhibitor–naive. Approximately 38% of patients in the GP 16-week group were NS5A-experienced and NS3/4A inhibitor–naive.

Source: Clinical Study Reports[6,11-18] and product monograph.[2]

Outcomes

The primary outcome in all trials was the proportion of patients who achieved SVR 12, which was defined as HCV RNA below the lower limit of quantitation (LLOQ) 12 weeks after the last actual dose of the study drug. Other virologic outcomes reported included virologic failure, on-treatment virologic failure, and relapse.

In all trials except SURVEYOR-II, on-treatment virologic failure was defined as a confirmed increase in HCV RNA of more than 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA was below the LLOQ during treatment, or

HCV RNA ≥ the LLOQ at the end of treatment with at least six weeks of treatment. In SURVEYOR-II, on-treatment virologic failure was defined as confirmed HCV RNA ≥ LLOQ after HCV RNA was below the LLOQ during treatment, confirmed increase of more than 1 $\log_{10}$ IU/mL above nadir during treatment, or HCV RNA ≥ LLOQ at end of treatment with at least six weeks of treatment.

Relapse was defined as confirmed HCV RNA ≥ LLOQ between the end of treatment and 12 weeks after the last dose of the study drug among patients who completed treatment as planned, with HCV RNA below the LLOQ at the end of treatment. The breakdown of relapse versus reinfection was based on HCV population sequencing. To complete treatment, patients had to have received ≥ 52 days of the 8-week treatment, or ≥ 72 days of the 12-week treatment.

All trials except MAGELLAN-1 evaluated patient-reported outcomes as exploratory outcomes. The instruments used included the Short Form (36) Health Survey (SF-36), the EuroQol 5-Dimensions (EQ-5D) 3-Levels or 5-Levels (EQ-5D-3L or -5L) health state questionnaire, the Fatigue Severity Scale (FSS), and the Work Productivity and Activity Index – Hepatitis C (WPAI-HCV).

The SF-36 is a generic health-assessment questionnaire that has been used in clinical trials to measure health-related quality of life (HRQoL). It consists of eight domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS). All domains and summary scores are measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general, use a minimal clinically important difference (MCID) of 2 to 4 points for each domain or 2 to 3 points for the MCS and PCS has been reported in the literature.

The EQ-5D is a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments.[44,45] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, representing “no problems,” “some problems,” and “extreme problems,” respectively, whereas the EQ-5D-5L has five response levels: level 1 (“no problems”), level 2 (“slight problems”), level 3 (“moderate problems”), level 4 (“severe problems”), and level 5 (“extreme problems” or “unable to perform”), which is the worst response in the dimension. 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. Reported MCIDs for the 3L version of the scale have ranged from 0.033 to 0.074 for general use.[46] The MCID estimates for the index score for the 5L version in the Canadian population have a summarized mean of 0.056, and a summarized median of 0.056 (interquartile range 0.049 to 0.063).[47] The MCID for the EQ-5D-3L or -5L among CHC patients remains unknown.

The second part of the EQ-5D is a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.” Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day.

The FSS is a generic, unidimensional, psychometric instrument designed to assess the impact of fatigue over the past week. The FSS consists of a self-administered questionnaire comprising nine items, each using a seven-point Likert scale.[48,49] Each of the nine FSS items is designed to rate the extent of fatigue symptoms and their impact on patient functioning.[50] Responses can vary from strongly disagree (1) to strongly agree (7).[48,49] Scores should be reported as a total (the minimum and maximum scores are 9 and 63, respectively), but are also reported as a mean (minimum and maximum means of 1 or 7, respectively).[48,50,51] Lower scores indicate that fatigue has a lower effect on everyday life. The FSS also includes a VAS measured as a 100 mm horizontal line that provides a single-item measure of overall fatigue severity.[48,51] Estimates of the MCID, based on distributional methods, have suggested that an interpretable and meaningful improvement in fatigue occurs when there is an observed group mean change in FSS total score of between 0.33 and 0.82 in patients with CHC.[50]

The WPAI-HCV is an instrument used to measure the impact of a disease on work and on daily activities. It elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing of work was challenging, and the extent to which the patient was limited at work (work impairment) during the past seven days. The activity impairment domain refers to the impairment in daily activities other than work. The scores are presented as a percentage, with lower values indicating better quality of life. There is no known MCID or validity data for patients with hepatitis C. An MCID of 7% has been reported for patients with Crohn's disease.[52]

Treatment-emergent adverse events were defined as any event that began or worsened in severity on or after the first dose of the study drug and no more than 30 days after the last dose. Serious adverse events were not defined except in CERTAIN-2, which used the following: death; life-threatening adverse event; hospitalization or prolongation of hospitalization; congenital anomaly; persistent or significant disability or incapacity; or important medical event requiring medical or surgical intervention to prevent a serious outcome. Data on serious adverse events was collected for the 24 weeks following the end of treatment.

Statistical Analysis

Similar analysis methods were used in the trials, and details have been summarized in Table 15. Sample size or power calculations are listed in Table 16 (Appendix 4).

The percentage of patients who achieved SVR 12 and two-sided 95% CI were calculated using either the normal approximation to the binomial distribution or the Wilson's score method (if the SVR 12 rate was 100%). The Wilson's score method was used to calculate the two-sided 95% CI for relapse and virologic failure outcomes. These analyses were based on the intention-to-treat (ITT) population, unless otherwise specified. There was no control of multiplicity for virologic outcomes except in ENDURANCE-1, -2, and -3, which is described below.

A backward imputation method was used for patients missing values for SVR. If the nearest HCV RNA value after the missing SVR time-point window was unquantifiable or undetectable, then it was used to impute the HCV RNA value in the SVR window. If the patient was missing an HCV RNA value within the appropriate SVR window after performing backward imputation, then this value was imputed with an HCV RNA value from a local laboratory, if present; otherwise, the HCV RNA value was considered missing and was imputed as a failure. Any patient who started a new treatment for CHC was considered

a viral response failure at all time points after the start of the new HCV treatment. For relapse and virologic failure outcomes, if HCV RNA values from the central laboratory were missing, then data from the local laboratory were used, if available.

Patient-reported outcomes were reported descriptively (mean, standard deviation [SD]) or analyzed using analysis of covariance (ANCOVA) models with treatment group and baseline score as covariates. Some of the trials reported on methods to handle missing items within an instrument (e.g., missing items in the FSS were imputed with the average score of answered items as long as more than 50% of items were answered [Table 15]). It appears that only patients who completed an instrument at a given time point were included in the analysis, with no methods applied to impute patients with missing data (e.g., last observation carried forward [LOCF]). There was no control of multiplicity for patient-reported outcomes in any of the studies.

The primary objective of ENDURANCE-1 was to show the noninferiority in terms of SVR 12 of GP for 12 weeks versus a historical control of sofosbuvir/ledipasvir or ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin for 12 weeks in DAA-naive, non-cirrhotic patients mono-infected with HCV genotype 1 (excluding those with HIV coinfection or who had failed to respond to prior sofosbuvir/ribavirin-based treatment). The SVR 12 rate for ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin was 97% (870 of 894 patients) and was based on data from phase III trials (trial details not specified), and the SVR 12 rate for sofosbuvir/ledipasvir (97%) was based on the data from the non-cirrhotic, DAA treatment-naive patients from the ION-1, ION-2, and ION-3 trials. To establish noninferiority to the historical control, a margin of 6% was applied to the historical control rate of 97%, resulting in a threshold of 91%. Thus, GP for 12 weeks was deemed noninferior to control if the lower bound of the 95% CI was greater than 91%. The 6% noninferiority margin was based on data comparing ombitasvir/paritaprevir/ritonavir plus dasabuvir ± ribavirin with boceprevir or telaprevir plus peg-IFN, and preserves 68% of the benefit of the DAA regimen over boceprevir or telaprevir. The secondary outcomes in ENDURANCE-1 were to determine the noninferiority of GP 8 weeks versus GP 12 weeks based on the per-protocol population, and based on the ITT population (excluding HIV and sofosbuvir/ribavirin treatment-experienced patients). A noninferiority margin of 5% was selected for these comparisons, and the sponsor stated this was to ensure a minimal loss of efficacy of the 8-week group relative to the 12-week group. A fixed-sequence testing procedure was used to control type I error, and testing of the second and third outcomes was to proceed only if noninferiority for the preceding outcomes was met. All other outcomes were outside the fixed-sequence testing procedure.

The primary objective of the ENDURANCE-2 study was to determine the noninferiority of GP 12 weeks versus the historical control of sofosbuvir/ribavirin 12 weeks in DAA-naive, non-cirrhotic patients with genotype 2 HCV infection. The SVR 12 rate of 95% for the sofosbuvir/ribavirin control was based on subgroup data from the FISSION,[53] POSITRON,[54] FUSION,[54] VALENCE,[55] and GS-US-344-0118 studies.[56] A 6% noninferiority margin was selected based on data comparing sofosbuvir/ribavirin with peg-IFN and preserved 68% of the difference between these treatments. Thus, for GP 12 weeks to meet the noninferiority criteria, the lower limit of the 95% CI had to exceed 89%. The secondary objective was to determine the superiority of GP to sofosbuvir/ribavirin (determined if the lower limit of 95% CI was > 95%). A fixed-testing procedure was applied and testing for superiority was conducted only if the primary noninferiority outcome was met. All other outcomes were outside the fixed-sequence testing procedure.

The primary objective of ENDURANCE-3 was to demonstrate noninferiority in the percentage of non-cirrhotic treatment-naive genotype 3 patients achieving SVR 12 with GP 12 weeks versus sofosbuvir plus daclatasvir 12 weeks. Noninferiority was met if the lower bound of the 95% CI of the difference between treatments was above −6%, or if the lower bound of 95% CI for the GP 12-week group was great than 92%. The 6% noninferiority margin preserved 80% of the benefit of sofosbuvir/daclatasvir compared with peg-IFN treatment. The same noninferiority criteria were applied to the analysis comparing GP 8 weeks with GP 12 weeks. Noninferiority was tested first with the ITT population and repeated with the per-protocol population. If noninferiority of GP 12 weeks versus sofosbuvir/daclatasvir was met, then superiority was tested. GP 12 weeks was superior if the lower bound of the 95% CI for the difference between treatments was greater than 0%. A Hochberg procedure was used to control for multiplicity. All other outcomes were outside the fixed-sequence testing procedure.

In CERTAIN-2, the primary efficacy end point was the noninferiority of GP 8 weeks versus sofosbuvir/ribavirin 12 weeks in terms of SVR 12, based on a noninferiority margin of −10%. If the lower bound of the CI for the difference was above the noninferiority margin of –10%, then GP was considered noninferior to sofosbuvir/ribavirin. The sponsor reported that the 10% margin was selected because it was similar to the 10.5% noninferiority margin used in previous clinical trials of first-generation IFN-free regimens. No further details were provided.

The analysis of SVR 12 in DAA-naive non-cirrhotic genotype 2 patients in the SURVEYOR-II Part 4 study was also compared with a historical control group (sofosbuvir/ribavirin 12 weeks). Based on a 95% SVR 12 rate for the control group and a 6% noninferiority margin, GP 8 weeks was deemed noninferior to sofosbuvir/ribavirin if the lower bound of the 95% CI was greater than 89%.

Analysis Populations

In all the trials, the efficacy analyses were based on the ITT population, which was defined as all enrolled patients who received at least one dose of the study drug. The exceptions are listed below:

- In ENDURANCE-1, the primary efficacy analyses were performed on the ITT subset of mono-infected HCV, DAA-naive patients (ITT primary subset [ITT-PS]). Noninferiority of 8-week GP versus 12-week GP was analyzed based on the per-protocol population. (i.e., all patients in the ITT-PS population, excluding those who discontinued treatment prematurely or who experienced virologic failure prior to week 8, those who had no HCV RNA value in the SVR 12 visit window or later). Non-inferiority of the 8-week GP versus 12-week GP was also analyzed based on the ITT-PS population.
- In the ENDURANCE-2 trial, the primary and key secondary efficacy analysis (virologic failure, relapse) excluded patients with prior sofosbuvir/ribavirin ± peg-IFN treatment failure.
- In SURVEYOR-II Part 4, the primary hypothesis testing (noninferiority) was based on the cohort of patients with genotype 2 HCV infection who were DAA-naive (i.e., excluding those with prior sofosbuvir/ribavirin ± peg-IFN treatment experience).

In ENDURANCE-3, the per-protocol population for the comparison of GP 12 weeks with sofosbuvir/daclatasvir included all patients in the ITT analysis, excluding those who did not have HCV genotype 3 infection, were nonresponders due to reinfection, or had missing follow-up data in the SVR 12 visit window. Patients who were nonresponders due to virologic failure or the premature discontinuation of the study drug were included. Patients

were analyzed based on the treatment received. The per-protocol population for the comparison of GP 8 weeks with GP 12 weeks included those in the ITT analysis, except for those who discontinued prior to week 8 (< 52 days) or had virologic failure prior to week 8, patients with no HCV RNA data in the SVR 12 visit window or later, and those with reinfection or who did not have genotype 3 HCV infection.

All of the trials also defined a modified ITT (mITT) population that included enrolled patients who received at least one dose of the study drug, excluding those who did not achieve SVR 12 due to a non-virologic reason (e.g., discontinued treatment, reinfection, missing data), or those with an ineligible HCV genotype. This population was used in the analysis of SVR 12 for subgroups with drug-resistant viral variants present at baseline.

In all trials, the safety analysis was based on all enrolled patients who received at least one dose of the study drug. In ENDURANCE-2 and ENDURANCE-3, the patient grouping was based on the actual treatment received, not the group to which the patient was randomized.

Patient Disposition

The number of patients screened for inclusion in the trials ranged from 140 to 807 patients, of which 11% to 45% failed to meet the study criteria and were not enrolled (

Table 9). For the vast majority of patients in all studies, the reason for screening failure was related to inclusion or exclusion criteria. The number of patients enrolled per treatment group ranged from 22 to 352 and, in total, 2,180 patients received GP. Few patients discontinued GP treatment (0% to 8.5%). The trial that enrolled DAA treatment–experienced patients (MAGELLAN-1 Part 2) had the highest withdrawal rate, with 4 of 47 patients (8.5%) stopping treatment due to lack of efficacy. In the three randomized controlled trials (RCTs), the percentage of patients who stopped treatment was similar between groups.

Table 9: Patient Disposition

	ENDURANCE-1		ENDURANCE-2		ENDURANCE-3			ENDURANCE-4
	GP 12 Weeks	**GP 8 Weeks**	**GP 12 Weeks**	**PBO 12 Weeks**	**GP 12 Weeks**	**SOF + DCV 12 Weeks**	**GP 8 Weeks**	**GP 12 Weeks**
Screened, N **Screen failure, N (%)**	807 103 (13%)		342 38 (11%)		603 97 (16%)			140 140 (14%)
Randomized, N (%)	352	352	204	100	233	116	–	–
Enrolled, N (%)	–	–	–	–	–	–	157	121
Enrolled and treated, N (%)	352	351	202	100	233	115	157	121 (100)
Completed treatment, N (%)	351	349	201	100	225	112	154	118 (98)
Discontinued drug, N (%)	1 (0.3)	2 (0.6)	1 (0.5)	0	8 (3.4)	3 (2.6)	3 (1.9)	3 (2.5)
Adverse events	1 (0.3)	0	0	0	3 (1.3)	1 (0.9)	0	2 (1.7)
Lost to follow-up	0	0	0	0	1 (0.4)	1 (0.9)	1 (0.6)	0
Withdrew consent	0	0	0	0	1 (0.4)	0	0	0
Lack of efficacy / virologic failure	0	1 (0.3)	0	0	0	0	0	0
Non-compliance	0	1 (0.3)	1 (0.5)	0	2 (0.9)	0	0	1 (0.8)
Other	0	0	0	0	1 (0.4)	1 (0.9)	2 (1.3)	0

	ENDURANCE-1		ENDURANCE-2		ENDURANCE-3			ENDURANCE-4
	GP 12 Weeks	GP 8 Weeks	GP 12 Weeks	PBO 12 Weeks	GP 12 Weeks	SOF + DCV 12 Weeks	GP 8 Weeks	GP 12 Weeks
Discontinued study, N (%)	1 (0.3)	3 (0.9)	2 (1.0)	NA	6 (2.6)	2 (1.7)	2 (1.3)	1 (0.8)
ITT, N	352	351	202	100	233	115	157	121
ITT-PS, N	332[a]	335[a]	196[b]	NA	NA	NA	NA	NA
Safety, N	352	351	202	100	233	115	157	121

Table 9: Patient Disposition (Continued)

	EXPEDITION-1	EXPEDITION-4	MAGELLAN-1 Part 2		CERTAIN-2	
	GP 12 Weeks	GP 12 Weeks	GP 12 Weeks	GP 16 Weeks	GP 8 Weeks	SOF + RBV 12 Weeks
Screened, N **Screen failure, N (%)**	242 96 (40%)	140 36 (26%)	163 72 (45%)		164 28 (17%)	
Randomized, N (%)	–	–	44	47	90	46
Enrolled, N (%)	146 (60)	104	–	–	–	–
Enrolled and treated, N (%)	146	104	44	47	90	46
Completed treatment, N (%)	144 (99)	100 (96)	44 (100)	43 (91)	89 (99)	45 (98)
Discontinued drug, N (%)	2 (1.4)	4 (3.8)	0	4 (8.5)	1 (1.1)	1 (2.2)
Adverse events	0	4 (3.8)			1 (1.1)	0
Lost to follow-up	0	0			0	0
Withdrew consent	0	0			0	1 (2.2)
Lack of efficacy / virologic failure	0	0		4 (8.5)	0	0
Non-compliance	0	0			0	0
Other	2 (1.4)				0	0
Discontinued study, N (%)	3 (2.1)	1 (1.0)	1 (2.3)	0	2 (2.2)	1 (2.2)
ITT, N	146	104	44	47	90	46
Safety, N	146	104	44	47	90	46

Table 9: Patient Disposition (Continued)

	SURVEYOR-II Part 3				SURVEYOR-II Part 4	
	GP 12 Weeks G 3 TE No Cirrhosis	GP 16 Weeks G 3 TE No Cirrhosis	GP 12 Weeks G 3 TN Cirrhosis	GP 16 Weeks G 3 TE Cirrhosis	GP 8 Weeks G 2	GP 8 Weeks G 4–6
Screened, N	NR[c]					
Randomized, N (%)	22	22	–	–	–	–
Enrolled, N (%)	–	–	40	48	145	58
Enrolled and treated, N (%)	22	22	40	47 (98)	145	58
Completed treatment, N (%)	22	22	39 (98)	46 (98)	144 (99)	57 (98)
Discontinued drug, N (%)	0	0	1 (3)	1 (2)	1 (1)	1 (2)
Adverse events						
Lost to follow-up					1 (1)	
Withdrew consent						
Lack of efficacy/virologic failure						
Non-compliance			1 (3)			1 (2)

	SURVEYOR-II Part 3				SURVEYOR-II Part 4	
	GP 12 Weeks G 3 TE No Cirrhosis	GP 16 Weeks G 3 TE No Cirrhosis	GP 12 Weeks G 3 TN Cirrhosis	GP 16 Weeks G 3 TE Cirrhosis	GP 8 Weeks G 2	GP 8 Weeks G 4–6
Discontinued study, N (%)	0	0	0	1 (2)	0	1 (2)
ITT, N	22	22	40	47	145	58
ITT-PS, N	NA	NA	NA	NA	137[d]	58
Safety, N	22	22	40	47	145	58

DCV = daclatasvir; G = genotype; GP = glecaprevir/pibrentasvir; ITT = intention to treat; ITT-PS = intention-to-treat primary subset; NA = not applicable; NR = not reported; PBO = placebo; RBV = ribavirin; TE = treatment-experienced; TN = treatment-naive; SOF = sofosbuvir.
[a] Primary analysis population excluded patients with HIV coinfection and history of prior DAA therapy (N = 36).
[b] Primary analysis excluded patients who had previously received SOF + RBV ± peg-IFN (N = 6).
[c] A total of 382 patients failed screening among all four parts of the SURVEYOR-II study. No information was provided specifically for Part 3 and 4.
[d] Analysis of noninferiority in genotype 2 patients excluded those with prior SOF/RBV treatment experience (N = 6) and those found to have genotype 1 HCV infection (N = 2).
Source: Clinical Study Reports.[6,11-18]

Exposure to Study Treatments

The vast majority of patients completed the planned treatment duration and the median treatment duration was 56 to 57 days for the 8-week groups, 84 to 85 days for the 12-week groups, and 113 days for the 16-week groups (Table 10).

Table 10: Duration of Exposure

Study	Treatment Group	Treatment Duration (Days)	
		Mean (SD)	Median (Range)
ENDURANCE-1	GP 8 weeks	56.3 (3.1)	56 (2 to 61)
	GP 12 weeks	84.3 (0.9)	84 (78 to 90)
ENDURANCE-2	GP 12 weeks	84.4 (2.8)	84 (47 to 90)
	Placebo 12 weeks	84.4 (0.6)	84 (82 to 86)
ENDURANCE-3	GP 8 weeks	56.1 (3.7)	56 (29 to 61)
	GP 12 weeks	83.3 (9.4)	85 (5 to 89)
	SOF/DCV 12 weeks	83.6 (6.8)	84 (12 to 91)
ENDURANCE-4	GP 12 weeks	83.3 (8.9)	84 (12 to 87)
MAGELLAN-1 Part 2	GP 12 weeks	84.5 (0.9)	84.5 (83 to 87)
	GP 16 weeks	109.1 (12.6)	113 (46 to 115)
SURVEYOR-II Part 3	GP 12 weeks G 3 TE no cirrhosis	85.1 (1.6)	85 (83 to 91)
	GP 16 weeks G 3 TE no cirrhosis	112.9 (0.8)	113 (111 to 114)
	GP 12 weeks G 3 TN cirrhosis	85.0 (2.6)	85 (71 to 88)
	GP 16 weeks G 3 TE cirrhosis	112.4 (4.5)	113 (83 to 116)
SURVEYOR-II Part 4	GP 8 weeks G 2	56.5 (3.7)	57 (15 to 64)
	GP 8 weeks G 4, 5, 6	57.0 (3.3)	57 (36 to 67)

Study	Treatment Group	Treatment Duration (Days)	
		Mean (SD)	Median (Range)
EXPEDITION-1	GP 12 weeks	83.9 (4.6)	84 (43 to 89)
EXPEDITION-4	GP 12 weeks	83.5 (6.3)	84 (27 to 87)
CERTAIN-2	GP 8 weeks	55.5 (4.0)	56 (18 to 57)
	SOF/RBV 12 weeks	82.4 (10.6)	84 (12 to 84)

DCV = daclatasvir; G = genotype; GP = glecaprevir/pibrentasvir; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive.
Source: Clinical Study Reports.[6,11-18]

Critical Appraisal

Internal Validity

Of the 10 included studies, only two were RCTs (CERTAIN-2 and ENDURANCE-3), which were designed to assess the noninferiority of GP versus an active control group. The other randomized trial (ENDURANCE-2) compared GP with placebo for the assessment of safety only. Three other trials randomized patients to groups; however, the comparators were other GP treatment regimens. In those studies, the method of randomization (interactive response technology) was sufficiently reported and deemed appropriate, and the patient characteristics appear to be similar between groups.

Six of the 10 studies were uncontrolled or assigned some patients to groups non-randomly. The ENDURANCE-3 study had three treatment groups, but only patients in the GP 12-week and sofosbuvir/daclatasvir groups were randomly allocated. Patients were assigned to the GP 8-week group once enrolment in the other two treatment groups was complete, and this lack of random allocation should be considered when interpreting the noninferiority analysis of GP 8 weeks versus GP 12 weeks. ENDURANCE-1, ENDURANCE-2, and SURVEYOR-II Part 4 share the same limitations related to comparisons with a historical control rather than a direct comparison between trial arms, which limits the ability to assess differences between the randomized treatments because of possible changes in clinical practice (i.e., standard of care) between the trials in the submission and the trials from which the historical control rates were derived, and because the characteristics of the patient populations from different time periods may not be similar. The selected historical control group in ENDURANCE-1 (ombitasvir/paritaprevir/ritonavir plus dasabuvir ± ribavirin or sofosbuvir/ledipasvir for 12 weeks) was clinically relevant for patients with genotype 1 HCV, but in ENDURANCE-2 and SURVEYOR-II Part 4, the selected control (sofosbuvir/ribavirin for 12 weeks) may be considered suboptimal by current treatment standards for those with genotype 2 HCV infection.[3,4] Although the full details on the historical control data were not reported, it appears that subgroup data for non-cirrhotic patients who were either treatment-naive or had prior IFN-based therapy were pooled. Simple methods were used to pool the data (i.e., the number of patients with SVR 12 and total number of patients per study subgroup were summed), rather than more robust methods, such as propensity score matching.

Except for the first 12 weeks of ENDURANCE-2, all trials were open-label studies. Being aware of treatment allocation may have influenced subjective measures, such as quality of life and reporting of adverse events. In ENDURANCE-2, patients received GP or matching placebo during the double-blind period, and an unblinded, independent external consultant monitored laboratory results and HCV RNA values for individual patients to maintain

blinding. There was no clear pattern of adverse effects observed that may have led to significant unblinding in this trial.

The vast majority of patients completed the treatments, with 0% to 3.8% of patients stopping treatment prematurely, except in MAGELLAN-1 Part 2, where four (8.5%) of DAA treatment–experienced patients stopped treatment early due to lack of efficacy.

All trials used an mITT population in the analysis of virologic outcomes, which consisted of patients who were enrolled in the study and received at least one dose of the study drug. Although this was not a true ITT population, in total, only five of the 2,447 patients enrolled did not receive treatment. ENDURANCE-1 and ENDURANCE-2 further limited the population for the primary outcome analysis by excluding those with prior sofosbuvir/ribavirin treatment experience or HIV coinfection. Although not specified, these exclusions may have been made to make the study groups more similar to the historical control groups. Data from the historical control studies included data for non-cirrhotic patients who were treatment-naive or had prior IFN-based therapy. The CERTAIN-2 study did not conduct analyses using a per-protocol population. The per-protocol analysis may be considered a more methodologically robust and conservative estimate, and concordance between the ITT and per-protocol analysis is needed to determine noninferiority. In ENDURANCE-3, different criteria were used to define the per-protocol population in the comparison between GP 12 weeks and daclatasvir/sofosbuvir and for GP 8 weeks versus GP 12 weeks. No rationale for these differences was provided and it is not clear if the per-protocol population for the GP 8-week to GP 12-week comparison was specified a priori. It is unclear what impact these differences may have had on the findings, especially considering the other limitations of this trial (i.e., GP 8-week group was not randomly assigned).

Four trials evaluated noninferiority based on a −6% margin for GP versus sofosbuvir/daclatasvir or a historical control group. The 6% was chosen to retain approximately two-thirds of the benefit of the selected historical control over the previous standard therapy. The ENDURANCE-1 study also used a −5% noninferiority margin to compare the GP 8-week and GP 12-week groups. This value was selected to minimize the loss of efficacy between treatments. The clinical expert consulted for this review stated that differences of less than 5% to 7% in SVR 12 are considered to be clinically unimportant; thus, the chosen noninferiority margins are likely reasonable. The CERTAIN-2 study evaluated noninferiority for GP 8 weeks versus sofosbuvir/ribavirin 12 weeks based on a 10% noninferiority margin. This margin may be considered overly large.

SVR 12 was the primary end point in all trials, which is a relevant outcome to patients with hepatitis C. Objective criteria were used to determine virologic end points and these were unlikely to be impacted by the lack of blinding. In all trials, imputation methods used for missing HCV RNA data for the SVR seemed appropriate. In three trials, there was a fixed statistical-testing procedure for the key outcomes (mainly noninferiority or superiority versus concurrent or historical comparator), but not for other important outcomes such as quality of life. None of the trials were designed to assess longer-term outcomes, such as hepatic-related morbidity or mortality, which are important to patients. Numerous subgroup analyses were conducted in all trials and although these were specified a priori, these data should be interpreted with caution given that the trials were not designed or powered for testing subgroup effects, and sample sizes were small for many of the subgroups.

Patient-reported outcomes (SF-36, EQ-5D, FSS, or WPAI-HCV) were exploratory efficacy end points in nine of the trials. The analyses appear to be based on the available case data, and the extent of missing data was between 1% and 15% for most instruments. Patients are

unlikely to be missing at random and, usually, it is sicker patients who are missing, which could lead to an overestimate in HRQoL or other patient-reported outcomes. Data were reported descriptively (within-group change) for five studies and, inferentially (as between-group difference), for four studies. There were no multiplicity adjustments applied to these end points.

The duration of GP treatment was not consistent with Health Canada recommendations for some of the populations studied. For example, no patients in ENDURANCE-2 or ENDURANCE-4, and less than 38% of patients in EXPEDITION-4 and MAGELLAN-1 Part 2 received the duration of GP recommended by Health Canada. Sample sizes were small for some treatment groups, specifically the phase II studies: SURVEYOR-II Part 3 (22 to 47 patients), SURVEYOR-II Part 4 genotype 4 to 6 group (58 patients) and MAGELLAN-1 Part 2 (44 and 47 patients). In these groups, differences in one or two patients can have a substantial impact on virologic response rates. Limited data were available for some patient populations of interest, namely, those with genotype 5 or 6 HCV infection (N = 31 and 37, respectively), HIV coinfection (N = 23), DAA treatment–experienced (N = 91), and treatment-experienced genotype 3 patients (N = 89). None of the pivotal trials included patients who had undergone a liver transplant, or who had hepatitis B coinfection.

External Validity

Overall, the trials represent a chronic HCV population with milder liver disease, as most patients enrolled had a fibrosis stage of F0−F1; less than 20% had advanced fibrosis or cirrhosis (F3 or F4). Generalizability of trial results may be limited for more complex patients, as important concurrent conditions were listed as exclusion criteria in the trials. For example, patients with HIV coinfection were excluded from all but one study (N = 33). No patients who had undergone a transplant were included in the pivotal trials. Few patients with genotype 5 or 6 HCV infection were enrolled although, globally, the prevalence of these viral variants in most regions is low.[57] In total, 137 of the patients enrolled were Canadian (0% to 20% per study). One trial included patients with ESRD and supports the use of GP in these patients.

One trial enrolled DAA treatment–experienced patients who had genotype 1 HCV infection (total N = 91). Of these, approximately one-third received a GP regimen that was consistent with the Health Canada–approved treatment duration. Interpretation of the results of the ENDURANCE-2 (genotype 2), ENDURANCE-3 (genotype 3), and EXPEDITION-4 (ESRD) studies should take into consideration that the 12-week treatment with GP was longer than the 8-week regimen recommended for the non-cirrhotic patients enrolled.

Comparative data are lacking, as most trials did not include another DAA-based regimen as a control group. Of the two active-controlled randomized trials, one included a comparator (sofosbuvir/ribavirin) that is no longer the standard of care for patients with genotype 2 to 6 HCV infection, although at the time this trial was conducted, sofosbuvir/ribavirin may have been the accepted standard of care in Japan. In all the trials, the treatment duration was sufficient to determine virologic response but not to assess longer-term morbidity, mortality, and safety.

Efficacy

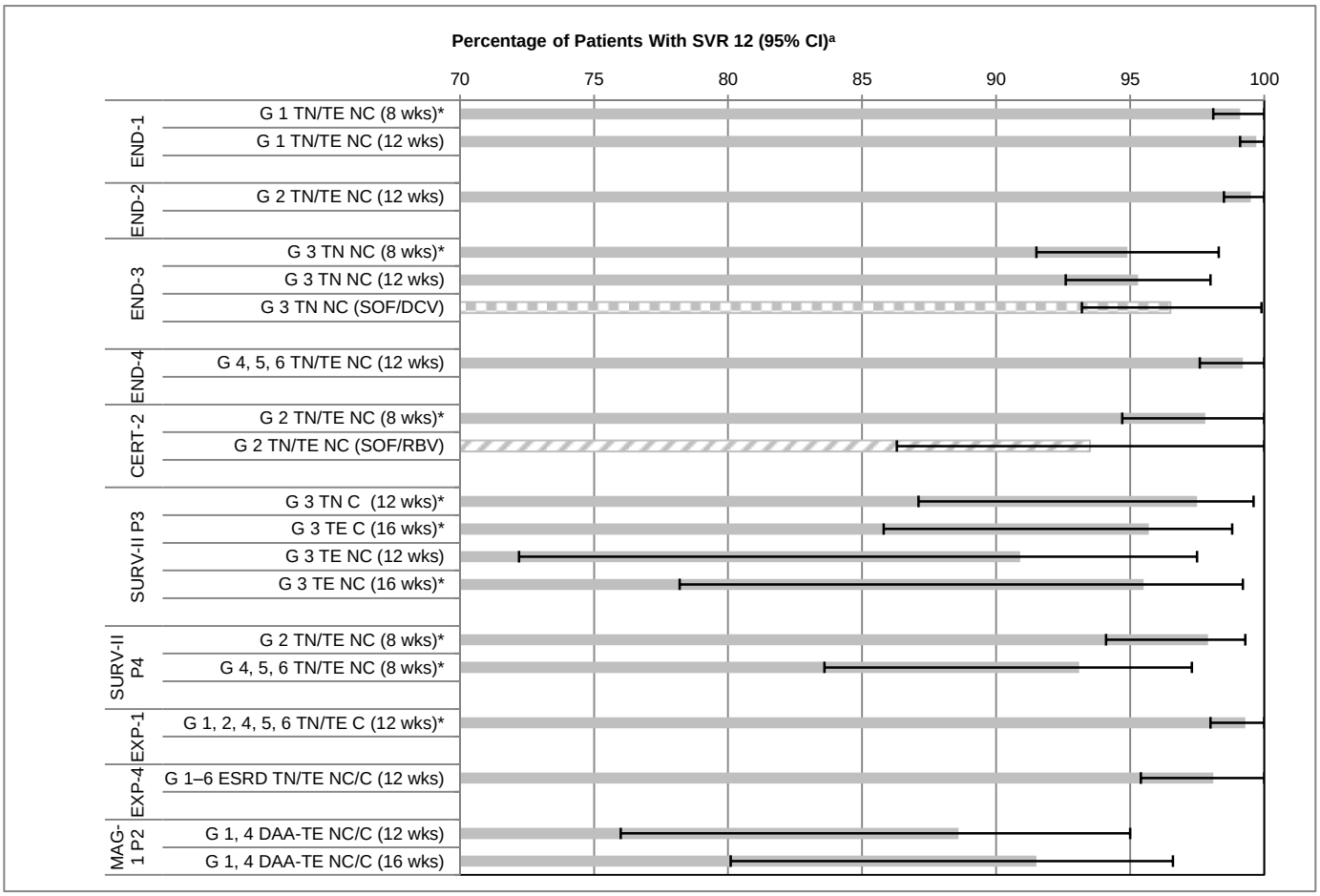
Only those efficacy outcomes identified in the review protocol (Table 4) are reported subsequently. See Appendix 4 for detailed efficacy data. Hepatic-related morbidity was an outcome of interest; however, the trials were not designed to assess the impact of treatment on longer-term hepatic disease.

Virologic Response

The percentage of patients achieving SVR 12 ranged from 88.6% to 99.7% among patients who received GP for 8, 12, or 16 weeks (Figure 3 and Table 11). In the GP treatment groups that enrolled only patients without cirrhosis, the SVR 12 rate ranged from 90.9% to 99.7% and, among those with cirrhosis, it ranged from 95.7% to 99.3%. Among the trials that enrolled a mixed population (cirrhotic and non-cirrhotic), the SVR 12 rate ranged from 88.6% to 98.1%. A complete listing of virologic response data, including subgroups, is found in Appendix 4 (Table 17).

Few patients experienced an on-treatment virologic failure or relapse (0 to 2 patients per group; < 1.5%) except for the study in patients with prior DAA-treatment failure (MAGELLAN-1 Part 2) and the genotype 3 patients in the ENDURANCE-3 or SURVEYOR-II studies. In the ENDURANCE-3 study, six patients (3.8%) in the GP 8-week group and four patients in the GP 12-week group (1.7%) experienced a relapse or on-treatment virologic failure compared with one patient in the sofosbuvir/daclatasvir groups (0.9%) (Table 11). In total, five of 90 (5.5%) treatment-experienced genotype 3 patients in SURVEYOR-II Part 3 experienced a relapse or on-treatment virologic failure; no treatment-naive genotype 3 patients relapsed. Other reasons for virologic failure across the treatment groups included premature discontinuation of study drug (0% to 2.2%) and missing SVR 12 data (0% to 5.2%). The reasons for virologic failure for the MAGELLAN-1 study is discussed subsequently.

Figure 3: SVR 12 Rate for Glecaprevir/Pibrentasvir Studies



C = cirrhosis; CERT-2 = CERTAIN-2; CI = confidence interval; DAA = direct-acting antiviral; DCV = daclatasvir; END-1 = ENDURANCE-1; END-2 = ENDURANCE-2; END-3 = ENDURANCE-3; END-4 = ENDURANCE-4; ESRD = end-stage renal disease; EXP-1 = EXPEDITION-1; EXP-4 = EXPEDITION-4; G = genotype; GP = glecaprevir/pibrentasvir; ITT = intention to treat; NC = no cirrhosis; MAG-1 P2 = MAGELLAN-1 Part 2; peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SURV-II P3 = SURVEYOR-II Part 3; SURV-II P4 = SURVEYOR-II Part 4; SVR 12 = sustained virologic response at 12 weeks; TE = treatment-experienced (IFN-based or SOF/RBV-based therapy unless otherwise specified); TN = treatment-naive; wk = week.

[a] ITT population except for ENDURANCE-1, which excluded patients with HIV coinfection or prior SOF/RBV ± peg-IFN treatment, and ENDURANCE-2, which excluded patients with prior SOF/RBV ± peg-IFN failure.

*All patients in the GP group received the Health Canada–recommended treatment duration.

Source: Clinical Study Reports.[6,11-18]

In ENDURANCE-1, the SVR 12 rate was 99.1% (95% CI, 98.1% to 100%) and 99.7% (95% CI, 99.1% to 100%) in non-cirrhotic genotype 1 patients in the GP 8-week and 12-week groups, respectively. GP 12 weeks met the noninferiority criteria, as the lower bound of the 95% CI was greater than 91% for the historical control. The primary analysis excluded patients with HIV coinfection and those who had prior sofosbuvir/ribavirin treatment (ITT-PS population), although all 36 of these patients achieved SVR 12. GP 8 weeks was noninferior to GP 12 weeks, as the lower limit of the 95% CI for the between-group difference was greater than −5% for the per-protocol (0.0%; 95% CI, −1.1 to 1.1%) and ITT-PS (−0.6%; 95% CI, −1.8% to 0.6%) populations. GP 8 weeks is the Health Canada–recommended treatment duration for this study's population.

Among genotype 2 patients without cirrhosis (treatment-naive or having had prior IFN-based therapy) who received GP for 12 weeks in the ENDURANCE-2 study, the SVR 12 rate was 99.5% (95% CI, 98.5% to 100%). GP for 12 weeks was noninferior to the historical control group (sofosbuvir/ribavirin), as the lower limit of the 95% CI was greater than 89%. GP 12 weeks also met the superiority criteria as defined in the trial (lower limit of 95% CI was greater than historical control SVR rate of 95%). The primary analysis excluded patients who had previously failed sofosbuvir/ribavirin-based therapy; however, all six of these patients achieved SVR 12. Of note, the treatment duration in ENDURANCE-2 was not consistent with the Health Canada–recommended duration of 8 weeks for this population.

In ENDURANCE-3, the percentage of treatment-naive, non-cirrhotic genotype 3 patients achieving SVR 12 was 96.5%, 95.3%, and 94.9% in the sofosbuvir/daclatasvir 12 weeks, GP 12 weeks, and GP 8 weeks groups, respectively. GP 12 weeks was noninferior to sofosbuvir/daclatasvir (SVR 12 difference: –1.2%; 95% CI, –5.6% to 3.1%, ITT) as the lower bound of the 95% CI was greater than the −6% noninferiority margin (Table 11). Similar results were found for the per-protocol population. Noninferiority was also achieved based on the absolute criterion, as the lower bound of the 95% CI for the SVR 12 rate in the GP 12-week group exceeded 92% (ITT and per-protocol). Superiority of GP 12 weeks versus sofosbuvir/daclatasvir was not met. GP 8 weeks also met the noninferiority criteria versus GP 12 weeks in the analysis of the ITT and per-protocol populations. Interpretation of these data should take into consideration that patients were assigned to the 8-week group, not randomly allocated. GP 8 weeks is the Health Canada–recommended treatment duration for this study's population.

CERTAIN-2 was designed to assess noninferiority of GP 8 weeks versus sofosbuvir/ribavirin 12 weeks in treatment-naive and treatment-experienced, non-cirrhotic patients with genotype 2 HCV infection. SVR 12 rates were 97.8% and 93.5% in the GP and sofosbuvir/ribavirin groups, respectively, with a difference between treatments of 4.3% (95% CI, −3.5% to 12.1%). The lower bound of the 95% CI was above the −10% noninferiority margin; thus, GP 8 weeks was deemed noninferior to sofosbuvir/ribavirin based on the ITT population. No per-protocol analysis was conducted.

In ENDURANCE-4, 99.2% (95% CI, 97.6% to 100%) of genotype 4, 5, or 6 patients achieved SVR 12 after 12 weeks of GP. One patient stopped treatment early and was considered a virologic failure. The Health Canada–recommended treatment duration is 8 weeks for these non-cirrhotic patients.

In SURVEYOR-II Part 3, the SVR 12 rate was 90.9% for non-cirrhotic treatment-experienced genotype 3 patients who received GP for 12 weeks, and 95.5% and 95.7% in the non-cirrhotic and cirrhotic patients, respectively, who received 16 weeks of GP therapy. Among the 22 patients who received 12 weeks of therapy, two patients (9.1%) relapsed. Health Canada recommends 16 weeks of treatment for treatment-experienced genotype 3 patients. The SVR 12 rate was 97.5% in treatment-naive cirrhotic genotype 3 patients. In Part 4, treatment-naive and treatment-experienced non-cirrhotic patients received GP for 8 weeks. The SVR 12 rate was 97.9% in patients with genotype 2 HCV infection and 93.1% in those with genotype 4 to 6 infection. Of the four patients with genotype 4 to 6 who did not achieve SVR 12, one had discontinued treatment and three had missing SVR 12 data; none experienced an on-treatment virologic failure or relapse.

All patients in the EXPEDITION-1 study had compensated cirrhosis and genotype 1, 2, 4, 5, or 6 HCV infection. Overall, 99.3% of patients (95% CI, 98% to 100%) achieved SVR 12 after 12 weeks of GP. One patient experienced a relapse.

Among patients with ESRD, the SVR 12 rate was 98% (95% CI, 95% to 100%), and no patients in the EXPEDITION-4 study had an on-treatment virologic failure or relapse. Of the two patients who did not achieve SVR 12, one discontinued treatment early and one had missing SVR 12 data. Of note, 17% of patients enrolled had cirrhosis and received the GP treatment duration recommended by Health Canada (12 weeks). Health Canada recommends 8 weeks of therapy for non-cirrhotic patients.[2]

In patients with genotype 1 or 4 CHC who had failed to respond to prior DAA-based therapy (MAGELLAN-1 Part 2), the SVR 12 rate was 88.6% (95% CI, 76.0% to 95.0%) in patients who received GP for 12 weeks and 91.5% (95% CI, 80.1% to 96.6%) in those who received 16 weeks of treatment. There were numerically more relapses in the 12-week group (n = 4, 9.3%) than in the 16-week group (n = 0), although the total number of patients with on-treatment virologic failure or relapse was similar (12 weeks: n = 5, 11.4%; 16 weeks: n = 4, 8.5%). Of note, Health Canada recommends 12 weeks of GP in genotype 1 CHC patients (with or without cirrhosis) who have experienced prior NS3/4A protease inhibitor treatment failure (simeprevir/sofosbuvir or pegylated interferon plus ribavirin combined with simeprevir, boceprevir, or telaprevir), and who are NS5A inhibitor–naive.[2] Sixteen weeks of therapy is recommended for genotype 1 CHC patients with prior NS5A treatment experience (either daclatasvir/sofosbuvir, daclatasvir plus pegylated interferon plus ribavirin [PR], or ledipasvir plus PR) and who are NS3/4A protease inhibitor–naive. GP is not recommended in patients who have been previously treated with a regimen of NS5A inhibitor with an NS3/4A protease inhibitor.[2] Subgroup data from MAGELLAN-1 were available based on prior treatment experience. Among patients who were NS3/4A inhibitor treatment–experienced (NS5A inhibitor–naive), all 14 patients in the 12-week group and all 13 patients in the 16-week GP treatment group achieved SVR 12 (Appendix 4, Table 17). In the GP 12-week and GP 16-week groups, 36% (N = 16) and 38% of patients (N = 18), respectively, had previously received an NS5A inhibitor (NS3/4A inhibitor–naive), and the SVR 12 rate in these subgroups was 88% and 94%, respectively. For patients who had previously received both classes of DAA, the SVR 12 rate was 79% and 81% in the 12-week and 16-week groups, respectively (total N = 30).

Table 11: Virologic Response

	ENDURANCE-1		ENDURANCE-2	ENDURANCE-3			CERTAIN-2	
	GP 12 Weeks	GP 8 Weeks	GP 12 Weeks	GP 12 Weeks	SOF/DCV 12 Weeks	GP 8 Weeks	GP 8 Weeks	SOF + RBV 12 Weeks
	N = 332[a]	N = 335[a]	N = 196 [b]	N = 233	N = 115	N = 157	N = 90	N = 46
SVR 12 n/N (%) [95% CI]	331 (99.7) [99.1 to 100]	332 (99.1) [98.1 to 100]	195/196 (99.5) [98.5 to 100.0]	ITT: 222/233 (95.3) [92.6 to 98.0] PP: 222/230 (96.5) [94.2 to 98.9]	ITT: 111/115 (96.5) [93.2 to 99.9] PP: 111/113 (98.2) [95.8 to 100.0]	ITT: 149/157 (94.9) [91.5 to 98.3] PP: 146/152 (96.1) [93.0 to 99.1]	ITT: 88/90 (97.8) [94.7 to 100.0] PP: NR	ITT: 43/46 (93.5) [86.3 to 100.0] PP: NR
Between-group difference (95% CI)	GP 12 wks – historical control[c] 2.4% (1.2% to 3.6%) GP 8 wks – GP 12 wks: –0.6% (–1.8% to 0.6%)[d] Historical control:[c] 870/894 (97.3%)		4.7% (2.3% to 7.2%) Historical control 361/381 (94.8%)	GP 12 wks – SOF/DCV: ITT: –1.2% (–5.6% to 3.1%) PP: –1.7% (–5.1% to 1.7%) GP 8 wks – GP 12 wks: ITT: –0.4% (–4.8% to 4.0%) PP: –2.2% (–5.7% to 1.4%)			ITT: 4.3 (–3.5 to 12.1) PP: NR	
Overall virologic failure, n/N (%)	1/332 (0.3)	3/335 (0.9)	1/196 (0.5)	11/233 (4.7)	4/115 (3.5)	8/157 (5.1)	2/90 (2.2)	3/46 (6.5)
Reason for nonresponse								
On-treatment virologic failure	0	1/335 (0.3)	0	1/233 (0.4)	0	1/157 (0.6)	0	0
Relapse	0	0	0	3/222 (1.4)	1/114 (0.9)	5/150 (3.3)	0	2/45 (4.4)
Premature discontinuation of treatment	0	1/335 (0.3)	0	4/233 (1.7)	1/115 (0.9)	0	1/90 (1.1)	1/46 (2.2)
HCV reinfection	0	0	0	0	0	0	0	0
Missing SVR 12 data	1/332 (0.3)	1/335 (0.3)	1/196 (0.5)	3/233 (1.3)	2/115 (1.7)	2/157 (1.3)	1/90 (1.1)	0
Other	0	0	0	0	0	0	0	0

Table 11: Virologic Response (Continued)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4	MAGELLAN-1 Part 2	
	GP 12 Weeks N = 121	**GP 12 Weeks N = 146**	**GP 12 Weeks N = 104**	**GP 12 Weeks N = 44**	**GP 16 Weeks N = 47**
SVR 12 N (%) [95% CI]	120 (99.2) [97.6 to 100.0]	145 (99.3) [98.0 to 100.0]	102 (98.1) [95.4 to 100.0]	39 (88.6) [76.0 to 95.0]	43 (91.5) [80.1 to 96.6]
P value	NA				
Overall virologic failure, n/N (%)	1/121 (0.8)	1/146 (0.7)	2/104 (1.9)	5/44 (11.4)	4/47 (8.5)
Reason for nonresponse					
On-treatment virologic failure	0	0	0	1/44 (2.3)	4/47 (8.5)
Relapse	0/118	1/144 (0.7)	0/100	4/43 (9.3)	0
Discontinued treatment	1/121 (0.8)	0	1/104 (1.0)	0	0
HCV reinfection	0	0	0	0	0
Missing SVR 12 data	0	0	1/104 (1.0)	0	0
Other	0	0	0	0	0

Table 11: Virologic Response (Continued)

	SURVEYOR-II Part 3				SURVEYOR-II Part 4	
Treatment Group	**GP 12 Weeks**	**GP 16 Weeks**	**GP 12 Weeks**	**GP 16 Weeks**	**GP 8 Weeks**	**GP 8 Weeks**
Population	**G 3 TE No Cirrhosis**	**G 3 TE No Cirrhosis**	**G 3 TN Cirrhosis**	**G 3 TE Cirrhosis**	**G 2 TN, TE No Cirrhosis**	**G 4, 5, 6 TN, TE No Cirrhosis**
Total N	**22**	**22**	**40**	**47**	**145[g]**	**58**
SVR 12 N (%) [95% CI]	20 (90.9) [72.2 to 97.5]	21 (95.5) [78.2 to 99.2]	39 (97.5) [87.1 to 99.6]	45 (95.7) [85.8 to 98.8]	142 (97.9) [94.1 to 99.3]	54/58 (93.1) [83.6 to 97.3]
P value						
Overall virologic failure, n/N (%)	2/22 (9.1)	1/22 (4.5)	1/40 (2.5)	2/47 (4.3)	3/145 (2.1)	4/58 (6.9)
Reason for nonresponse						
On-treatment virologic failure	0	0	0	1/47 (2.1)	0	0
Relapse	2/22 (9.1)	1/22 (4.5)	0	1/46 (2.2)	2/144 (1.4)	0/57
Discontinued treatment	0	0	0	0	1/145 (0.7)	1/58 (1.7)
HCV reinfection	0	0	0	0	0	0
Missing SVR 12 data	0	0	1/40 (2.5)	0	0	3/58 (5.2)
Other	0	0	0	0	0	0

CI = confidence interval; DAA = direct-acting antiviral; DCV = daclatasvir; G = genotype; GP = glecaprevir/pibrentasvir; HCV = hepatitis C virus; ITT = intention to treat; ITT-PS = intention-to-treat primary subset; LDV = ledipasvir; NR = not reported; peg-IFN = pegylated interferon; PP = per-protocol; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir; SVR 12 = sustained virologic response at 12 weeks; TE = treatment-experienced; TN = treatment-naive; wk = week.

[a] ITT-PS population (ITT subset of HCV mono-infected DAA-naive patients), which included 95% of treated patients.

[b] Excluding patients with prior SOF + RBV ± peg-IFN treatment failures (N = 6, 3%).

[c] Historical control was ombitasvir/paritaprevir/ritonavir + dasabuvir ± RBV or SOF/LDV for 12 weeks.

[d] Treatment difference for GP 8 weeks versus GP 12 weeks was 0.0 (95% CI, −1.1 to 1.1) based on the PP, mono-infected, and DAA-naive population. GP 8 weeks was noninferior to GP 12 weeks, as the lower limit of the 95% CI was greater than the −5% noninferiority margin.

[e] ITT population, imputation of missing data as failures.

[f] Categories based on creatinine clearance.

[g] SURVEYOR-II Part 4: Two genotype 2–infected patients who were later determined to be infected with genotype 1 were included in the ITT results but excluded from the comparison to historical control.

Source: Clinical Study Reports.[6,11-18]

SVR 12 rates according to the presence of drug-resistant variants at baseline were not reported for the SURVEYOR-II studies; data from other studies are summarized in Table 12. Data were reported for the mITT population that excluded patients who did not have the HCV genotype specified in the inclusion criteria, and those who did not achieve SVR 12 for reasons other than virologic failure. Among those with an NS3/4A- or NS5A-resistant variant present at baseline, the SVR 12 rates were 86% in patients in MAGELLAN-1 (DAA treatment–experienced). Rates ranged from 91% to 95% in ENDURANCE-3 (genotype 3) and 100% in other studies that reported these data.

Table 12: SVR 12 in Patients With Baseline NS5A- or NS3/4A-Resistant Variant (mITT)

	ENDURANCE-1		ENDURANCE-2	ENDURANCE-3			CERTAIN-2	
	GP 12 Weeks N = 352	GP 8 Weeks N = 352	GP 12 Weeks N = 202	GP 12 Weeks N = 233	SOF + DCV 12 Weeks N = 115	GP 8 Weeks N = 157	GP 8 Weeks N = 90	SOF + RBV 12 Weeks N = 46
SVR 12								
Total N	351[a]	349[a]	192[ab]	226[a]	112[a]	155[a]	90[a]	46[a]
Any NS3/4A variant, n/N (%)	1/1 (100)	6/6 (100)	0	3/ 4 (75)	0	1/ 2 (50)	1/1 (100)	NR
Any NS5A variant, n/N (%)	44/44 (100)	37/37 (100)	57/57 (100)	41/ 43 (95)	20/ 21 (95)	39/ 43 (91)	9/9 (100)	NR
NS3/4A or NS5A variant, n/N (%)	45/45 (100)	42/42 (100)	57/57 (100)	42/ 44 (95)	20/ 21 (95)	39/ 43 (91)	9/9 (100)	NR

Table 12: SVR 12 in Patients With Baseline NS5A- or NS3/4A-Resistant Variants (mITT) (Continued)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4	MAGELLAN-1 Part 2	
SVR 12	GP 12 Weeks N = 121	GP 12 Weeks N = 146	GP 12 Weeks N = 104	GP 12 Weeks N = 44	GP 16 Weeks N = 47
Total N	120[a]	145[a]	102[a]	44[a]	47[a]
Any NS3/4A variant, n/N (%)	13/13 (100)	4/4 (100)	1/1 (100)	6/7 (86)	5/8 (63)
Any NS5A variant, n/N (%)	27/27 (100)	28/29 (97)	17/17 (100)	21/25 (84)	20/24 (83)
NS3/4A or NS5A variant, n/N (%)	37/37 (100)	32/33 (97)	18/18 (100)	24/28 (86)	24/28 (86)

DCV = daclatasvir; G = genotype; GP = glecaprevir/pibrentasvir; mITT = modified intention to treat; mITT-GT-VF = modified ITT-genotype-virologic failure; NR = not reported; NS = nonstructural viral protein; RBV = ribavirin; SOF = sofosbuvir; SVR 12 = sustained virologic response.

[a] mITT-GT-VF population includes all patients in the ITT population, excluding patients who do not have that particular HCV genotype and the patients who did not achieve SVR 12 for reasons other than virologic failure.

[b] Excludes patients with prior exposure to SOF/RBV-based therapy.

Source: Clinical Study Reports.[6,11-18]

Health-Related Quality of Life

Seven trials reported HRQoL using the SF-36 (version 2) instrument and reported data for the individual domains, and the MCS and PCS. For this report, the MCS and PCS have been summarized in Appendix 4, Table 18. Seven trials reported the index score and VAS scores for the EQ-5D-3L (ENDURANCE-1, -2, -3, and -4, EXPEDITION-1 and -4, CERTAIN-2) and two trials reported the EQ-5D-5L (SURVEYOR-II Part 3 and 4) (Appendix 4, Table 19). No quality-of-life data were reported in the MAGELLAN-1 study. HRQoL was an exploratory outcome in all studies and most trials reported data descriptively, as the within-group change from baseline. Results were available for ≥ 88% of patients for the SF-36 and ≥ 87% for EQ-5D. In general use, 2 to 3 points for the SF-36 MCS and PCS, 0.033

to 0.074 on the EQ-5D-3L index score, and 0.056 on the EQ-5D-5L index score represent a meaningful change, as determined by the patient.[46,47]

At baseline, the mean SF-36 PCS score ranged from 41.6 to 51.3 across treatment groups and were similar between GP and placebo or sofosbuvir/daclatasvir groups in the controlled trials (ENDURANCE-2 and -3). The mean within-group change from baseline ranged from −0.4 points to 3.1 points at the final treatment visit, and from 0 to 3.5 points at the 12-week follow-up visit. No statistically significant differences were detected between GP and placebo or sofosbuvir/daclatasvir (Appendix 4, Table 18). The results were similar for the SF-36 MCS (mean baseline: 42.3 to 48.6; mean change from baseline to end of treatment: −1.8 to 2.9; mean change from baseline to 12-week follow-up: −0.4 to 4.4), with no statistically significant differences between GP and placebo or sofosbuvir/daclatasvir.

The mean EQ-5D index score at baseline was between 0.69 and 0.96 across treatment groups (Appendix 4, Table 19). The mean within-group change from baseline to end of treatment ranged from −0.04 to 0.04, and to the 12-week follow-up visit was −0.00 to 0.06. No statistically significant differences were detected between the GP and control groups (placebo, sofosbuvir/daclatasvir, or sofosbuvir/ribavirin) in the ENDURANCE-2, -3, or CERTAIN-2 studies. The mean EQ-5D VAS score ranged from 60.8 to 83.7 at baseline across trials and was similar between GP and control groups in ENDURANCE-2, -3, and CERTAIN-2. In the GP studies without an active control group, the mean change from baseline to the end of treatment ranged from 2.0 to 5.3, and from baseline to the 12-week follow-up visit ranged from 4.3 to 8.4. The least squares mean difference between GP and placebo or sofosbuvir/daclatasvir was not statistically significant. In CERTAIN-2, the least squares mean difference in the change from baseline for GP versus sofosbuvir/ribavirin was 7.1; 95% CI, 2.2 to 12.0, at the end of treatment, and −2.5; 95% CI, −6.3 to 1.2 at the 12-week follow-up visit.

Other Patient-Reported Outcomes

Eight studies reported data for the FSS and seven reported data for the WPAI-HCV (Appendix 4, Table 20). For the FSS total score, data were available for ≥ 89% of patients. The WPAI overall work impairment score was reported for 25% to 57% of patients enrolled, and the activity impairment score was reported for 85% to 99% of patients. Patient-reported outcomes were exploratory outcomes in all studies and most trials reported data descriptively as the within-group change from baseline. The MCID in patients with hepatitis C is not known for either instrument.

The mean total FSS score ranged from 3.0 points to 4.3 points at baseline and changed from −0.5 points to 0.25 points at the final treatment visit, and from −0.6 points to 0 points at the 12-week follow-up visit, across treatment groups. No statistically significant differences were detected between GP and placebo, sofosbuvir/daclatasvir, and sofosbuvir/ribavirin in the ENDURANCE-2, ENDURANCE-3, and CERTAIN-2 trials.

At baseline, the mean overall work impairment score for the WPAI-HCV instrument was lowest in the ENDURANCE-4 study (5.8) and highest in the SURVEYOR-II Part 3 GP 16-week patients (24.7). The change from baseline ranged from −10.0 (SURVEYOR-II Part 2; GP 12-weeks) to 3.3 (ENDURANCE-4) at the final treatment visit, and from −14.0 (ENDURANCE-3 sofosbuvir/daclatasvir group) to 1.6 (ENDURANCE-4) at the 12-week follow-up visit. The mean baseline WPAI-HCV activity impairment score ranged from 15.8 (ENDURANCE-2 GP group) to 31.6 (SURVEYOR-II Part 3; GP 12 weeks). The change from baseline to the end-of-treatment visit ranged from −14.2 to 4.4 and from −18.8 to −4.0

from baseline to the 12-week follow-up visit. No statistically significant differences were detected between GP and placebo or sofosbuvir/daclatasvir in the ENDURANCE-2 and ENDURANCE-3 studies for the WPAI-HCV overall work impairment or activity impairment scores.

Mortality

No deaths were reported in the ENDURANCE-2, ENDURANCE-4, SURVEYOR-II, MAGELLAN-1, or CERTAIN-2 trials.

One death was reported among GP-treated patients in each of the ENDURANCE-1, ENDURANCE-3, EXPEDITION-1, and EXPEDITION-4 studies. Two deaths were due to cerebral hemorrhage, one was an accidental overdose, and one had an unknown cause. One additional patient died in the sofosbuvir/daclatasvir group in ENDURANCE-3 (cause not specified).

Harms

Only those harms identified in the review protocol are reported below. See Table 13 for detailed harms data.

Adverse Events

The frequency of adverse events ranged from 48% to 76%, with headache (7% to 26%), fatigue (7% to 24%), and nausea (3% to 14%) reported most frequently in the GP groups (Table 13).

During the double-blind period in ENDURANCE-2, 65% of GP-treated patients and 58% of placebo patients experienced an adverse event. In ENDURANCE-3, 76%, 62%, and 70% of patients in the GP 12-week, GP 8-week, and sofosbuvir/daclatasvir groups, respectively, reported an adverse event. More patients in the sofosbuvir/ribavirin 12-week group (76%) experienced an adverse event than in the GP 8-week group (48%) in CERTAIN-2. In this trial, the frequency of anemia (35% versus 0%) and increased bilirubin (15.2% versus 1.1%) was higher in the sofosbuvir/ribavirin group compared with the GP group.

Serious Adverse Events

The frequency of serious adverse events among GP-treated patients ranged from 0.8% to 7.5%, except for EXPEDITION-4 (the trial that included patients with ESRD), in which 24% of patients reported a serious adverse event (Table 13). In EXPEDITION-4, three patients reported gastrointestinal hemorrhage, and two reported congestive cardiac failure. All other specific serious adverse events were reported in one patient.

Withdrawals Due to Adverse Events

Few patients stopped treatment due to adverse events in all treatment groups (0% to 3.8%). Withdrawals were highest in the trial in patients with ESRD (3.8%) (Table 13).

Mortality

In total, four deaths occurred among the 2,180 patients who received GP. One death was reported among patients who received sofosbuvir/daclatasvir (total N = 115), and no deaths

occurred among those who received placebo (N = 100) or sofosbuvir/ribavirin (N = 46) (Table 13).

Notable Harms

Grade 3 elevation in bilirubin (three times the upper limit of normal [ULN]) was reported in eight patients who received GP and one patient who received sofosbuvir/ribavirin (Table 13). Of these events, five were not associated with elevations in alanine aminotransferase (ALT), four were predominantly related to indirect bilirubin and four were isolated events. One patient in the SURVEYOR-II Part 3 trial had three events of grade 3 bilirubin elevation. This patient had grade 2 bilirubin elevation at baseline and the grade 3 events were not associated with elevations in ALT.

In the MAGELLAN-1 study, two patients had a serious adverse event of hepatocellular carcinoma. Both patients had cirrhosis and one had a history of benign hepatic nodules. Hepatocellular carcinoma was detected 37 days and 105 days after the last dose of the study drug was not considered to be related to the study drug for either patient. Two patients in EXPEDITION-1 had hepatocellular carcinoma on post-treatment day 8 and treatment day 40. Both patients had cirrhosis and the adverse event was not considered related to the study drug.

One patient in EXPEDITION-1 met the criteria for having a hepatic decompensation / hepatic failure event defined as: ascites, hepatic encephalopathy, esophageal variceal bleeding, or spontaneous bacterial peritonitis. The patient was 64 years old, with cirrhosis, a baseline Child-Pugh score of 6, and known esophageal varices, and experienced an event of esophageal varices hemorrhage on day 22. There were no other clinical signs of hepatic failure and no concurrent change in ALT, total bilirubin (direct and indirect), platelets, or international normalized ratio. The patient continued treatment and achieved SVR 12.

In ENDURANCE-1, one patient in the GP 12-week group met the criteria for hepatotoxicity defined as one of the following:

- confirmed ALT value > 5 × ULN and ≥ 2 × baseline
- post-nadir increase in ALT grade to grade 2 (ALT value > 3 × ULN) and a concurrent total bilirubin ≥ 2 × ULN with a direct-to-total bilirubin ratio of greater than 0.4.

The patient had grade 3 ALT, aspartate aminotransferase, and gamma-glutamyl transferase values, as well as elevation of alkaline phosphatase on day 87 (one day after the last dose of the study drug). The patient had also reported adverse events of diarrhea and abdominal pain, headache, pyrexia, and fatigue at some point during the treatment period. Although the biochemistry profile was consistent with a transient biliary tract obstruction, an ultrasound was not available at the time of the event. An ultrasound of the liver and biliary system performed after the liver chemistries had normalized revealed two gallstones without evidence of biliary dilatation.

Table 13: Harms

	ENDURANCE-1		ENDURANCE-2		ENDURANCE-3		
	GP 12 Weeks N = 352	GP 8 Weeks N = 351	GP 12 Weeks N = 202	PBO N = 100	GP 12 Weeks N = 233	SOF + DCV 12 Weeks N = 115	GP 8 Weeks N = 157
AEs							
Patients with ≥ 1 AEs, n (%)	234 (66.5)	216 (61.5)	131 (64.9)	58 (58.0)	177 (76.0)	80 (69.6)	98 (62.4)
Most common AEs[a]							
Headache	62 (17.6)	68 (19.4)	24 (12)	12 (12)	60 (25.8)	23 (20.0)	31 (19.7)
Fatigue	43 (12.2)	31 (8.8)	23 (11)	10 (10)	44 (18.9)	16 (13.9)	20 (12.7)
Nausea	29 (8.2)	19 (5.4)	15 (7)	3 (3)	32 (13.7)	15 (13.0)	19 (12.1)
Asthenia			19 (9)	8 (8)	4 (1.7)	7 (6.1)	3 (1.9)
Pruritus	17 (4.8)	20 (5.7)	12 (6)	6 (6)			
Diarrhea			20 (10)	3 (3)	15 (6.4)	4 (3.5)	18 (11.5)
Vomiting					10 (4.3)	5 (4.3)	9 (5.7)
Upper respiratory tract infection					15 (6.4)	4 (3.5)	2 (1.3)
Nasopharyngitis	31 (8.8)	22 (6.3)			12 (5.2)	7 (6.1)	4 (2.5)
Insomnia	15 (4.3)	21 (6.0)			9 (3.9)	6 (5.2)	0
SAEs							
Patients with ≥ 1 SAE, n (%)	4 (1.1)	5 (1.4)	3 (1.5)	1 (1.0)	5 (2.1)	2 (1.7)	3 (1.9)
Description	AF, irritable bowel syndrome, bronchitis, pneumonia, aspiration/ death (1 case per event)	Angina unstable, arterial injury / suicide attempt, radius fracture, uterine leiomyoma, TIA (1 case per event)	Hemorrhoids, ankle fracture / joint dislocation, bile duct stone (1 case per event)	Rheumatoid arthritis	Limb injury, pneumonia, paranasal sinus and nasal cavity malignant neoplasm (recurrent), acute respiratory failure and hypoxia, abortion (missed)	Substance-induced psychotic disorder, iron deficiency	Ophthalmic herpes simplex and ulcerative keratitis, dependence, accidental overdose, and poisoning

	ENDURANCE-1		ENDURANCE-2		ENDURANCE-3		
	GP 12 Weeks N = 352	GP 8 Weeks N = 351	GP 12 Weeks N = 202	PBO N = 100	GP 12 Weeks N = 233	SOF + DCV 12 Weeks N = 115	GP 8 Weeks N = 157
WDAEs							
AE leading to drug discontinuation, n (%)	1 (0.3)	0	0	0	3 (1.3)	1 (0.9)	0
Description	Dandruff/ anxiety/ amnesia				Nausea/ diarrhea/ dizziness/ fatigue/ malaise/ abdominal pain and headache, paranasal sinus, and nasal cavity malignant neoplasm (recurrent), alcohol abuse	Headache	
Deaths							
n (%)	1 (0.3)	0	0	0	0	1 (0.9)	1 (0.6)
Description	Unknown cause					No specified	Accidental overdose
Notable Harms							
Anemia	NR	NR	NR	NR	NR	NR	NR
Total bilirubin ≥ 3× ULN	1 (0.3)	2 (0.6)	1 (0.5)	0	0	0	1 (0.6)
Hepatotoxicity[b]	0	0	1 (0.5)	0	0	0	0
Hepatic decompensation or hepatic failure events	0	0	0	0	0	0	0
Hepatocellular carcinoma	0	0	0	0	0	0	0

Table 13: Harms (Continued)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4
	GP 12 Weeks N = 121	GP 12 Weeks N = 146[a]	GP 12 Weeks N = 104
AEs			
Patients with ≥ 1 AEs, n (%)	83 (69)	101 (69)	74 (71)
Most common AEs[a]			
Headache	25 (21)	20 (14)	9 (9)
Fatigue	21 (17)	28 (19)	15 (14)
Nausea	12 (10)	13 (9)	12 (12)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4
	GP 12 Weeks N = 121	GP 12 Weeks N = 146[a]	GP 12 Weeks N = 104
Asthenia	11 (9)		10 (10)
Pruritus	10 (8)	14 (10)	21 (20)
Diarrhea	8 (7)	12 (8)	10 (10)
Urinary tract infection		9 (6)	
Decreased appetite			9 (9)
Vomiting			7 (7)
Dizziness			6 (6)
Dyspnea			6 (6)
SAEs			
Patients with ≥ 1 SAEs, n (%)	1 (0.8)	11 (7.5)	25 (24)
Description	TIA	HCC (2 cases); all other events occurred in a single patient	Gastrointestinal hemorrhage (3 cases), congestive cardiac failure (2); all other events occurred in a single patient
WDAEs			
AE leading to drug discontinuation, n (%)	3 (2.5)	0	4 (3.8)
Description	Anxiety, TIA, dyspepsia		
Deaths			
n (%)	0	1 (0.7)	1 (1.0)
Description		Cerebral hemorrhage	Cerebral hemorrhage
Notable harms			
Anemia	NR	2 (1.4)	3 (2.9)
Total bilirubin ≥ 3× ULN	0	0	1 (1.0)
Hepatotoxicity[b]	0	0	0
Hepatic decompensation or hepatic failure events	0	1 (0.7)	0
Hepatocellular carcinoma	0	2 (1.4)	0

Table 13: Harms (Continued)

	SURVEYOR-II Part 3		SURVEYOR-II Part 4	MAGELLAN-1 Part 2		CERTAIN-2	
	GP 12 or 16 Weeks[c] No Cirrhosis N = 44	GP 12 or 16 Weeks[c] Cirrhosis N = 87	GP 8 Weeks[b] N = 203	GP 12 Weeks N = 44	GP 16 Weeks N = 47	GP 8 Weeks N = 90	SOF + RBV 12 Weeks N = 46
AEs							
Patients with ≥ 1 AEs, n (%)	29 (66)	66 (76)	128 (63)	33 (75)	32 (68)	43 (47.8)	35 (76.1)
Most common AEs[a]							
Headache	9 (21)	16 (18)	28 (14)	6 (14)	11 (23)	6 (6.7)	1 (2.2)
Fatigue	8 (18)	21 (24)	37 (18)	3 (7)	5 (11)		
Nausea	4 (9)	9 (10)	23 (11)	4 (9)	3 (6)	3 (3.3)	3 (6.5)
Asthenia				1 (2)	3 (6)		
Pruritus							
Diarrhea	3 (7)	5 (6)					

	SURVEYOR-II Part 3		SURVEYOR-II Part 4	MAGELLAN-1 Part 2		CERTAIN-2	
	GP 12 or 16 Weeks[c] No Cirrhosis N = 44	GP 12 or 16 Weeks[c] Cirrhosis N = 87	GP 8 Weeks[b] N = 203	GP 12 Weeks N = 44	GP 16 Weeks N = 47	GP 8 Weeks N = 90	SOF + RBV 12 Weeks N = 46
Abdominal pain	3 (7)	4 (5)					
Dizziness	1 (2)	5 (6)					
Upper respiratory tract infection	1 (2)	5 (6)	13 (6)	1 (2)	4 (9)		
Back pain	4 (9)	4 (5)					
Nasopharyngitis	2 (5)	5 (6)				9 (10.0)	5 (10.9)
Oropharyngeal pain	3 (7)	0					
Dyspnea				2 (5)	4 (9)		
Constipation				0	4 (9)		
Lethargy				3 (7)	1 (2)		
Stomatitis						1 (1.1)	3 (6.5)
Malaise						5 (5.6)	4 (8.7)
Bilirubin increase						1 (1.1)	7 (15.2)
SAEs							
Patients with ≥ 1 SAEs, n (%)	2 (5)	4 (5)	2 (1)	1 (2)	2 (4)	2 (2.2)	2 (4.3)
Description	Hernia, colon cancer, pleural effusion, squamous cell carcinoma, schizophrenia, angina pectoris		Cholecystitis, urosepsis	GI viral infection	Wound infection, back pain	Pneumothorax spontaneous, angina (unstable)	Pneumonia, Castleman's disease
WDAEs							
AE leading to drug discontinuation, n (%)	0	0	0	0	0	1 (1.1)	1 (2.2)
Description						Nausea and vomiting	Malaise
Deaths							
n (%)	0	0	0	0	0	0	0
Notable harms							
Anemia	NR	NR	1 (0.5)	NR	NR	0	16 (34.8)
Total bilirubin ≥ 3× ULN	0	1 (1)	1 (0.5)	0	0	0	1 (2.2)
Hepatotoxicity[b]	0	0	0	0	0	NR	NR
Hepatic decompensation or Hepatic failure events	0	0	0	0	0	0	0
Hepatocellular carcinoma	0	0	0	2 (4.5)	0	0	0

AE = adverse event; AF = atrial fibrillation; ALT = alanine aminotransferase; ARF = acute respiratory failure; DCV = daclatasvir; GI = gastrointestinal; GP = glecaprevir/pibrentasvir; HCC = hepatocellular carcinoma; IBS = irritable bowel syndrome; NR = not reported; PBO = placebo; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir; TIA = transient ischemic attack; ULN = upper limit of normal; WDAE = withdrawals due to adverse event.

[a] Frequency > 5% in at least one treatment group per study.

[b] ALT > 5 × ULN and ≥ 2 × baseline, or post-nadir increase in ALT to > 3 × ULN and total bilirubin ≥ 2 × ULN with a direct-to-total bilirubin ratio > 0.4).

[c] Pooled reporting of adverse events based on presence of cirrhosis. Direct bilirubin and total-value bilirubin.

Source: Clinical Study Reports.[6,11-18]

Discussion

Summary of Available Evidence

A total of nine reports presenting data from 10 unique studies were included in the review. Three trials were open-label single-group studies (EXPEDITION-1, EXPEDITION-4, ENDURANCE-4) and four trials were open-label studies that randomized or assigned patients to more than one GP treatment group (ENDURANCE-1, SURVEYOR-II Part 3 and Part 4, MAGELLAN-1 Part 2). Two trials were open-label RCTs (CERTAIN-2, ENDURANCE-3) and one trial was a randomized double-blind study (ENDURANCE-2).

Three trials (ENDURANCE-1, ENDURANCE-2, SURVEYOR-II Part 4) compared the SVR 12 rate of patients on GP with a historical control to determine noninferiority. Two controlled trials were designed to assess the noninferiority of GP 8 weeks versus sofosbuvir/ribavirin 12 weeks (CERTAIN-2), or GP 12 weeks versus sofosbuvir/daclatasvir 12 weeks (ENDURANCE-3). The double-blind RCT ENDURANCE-2 was designed to assess safety of GP 12 weeks versus placebo.

Patients with all genotypes were enrolled, including those who were treatment-naive (nine trials), had prior IFN-based or sofosbuvir/ribavirin-based treatment experience (eight trials), prior DAA-treatment experience (one trial), ESRD (one trial), or HIV coinfection (one trial). Patients with compensated cirrhosis were included in three trials and those without cirrhosis were included in nine trials. In total, 2,180 patients received GP.

The mean age per treatment group ranged from 45.4 years to 60.1 years, and the patients enrolled were predominantly white (60% to 93%), except in CERTAIN-2, in which all patients were Japanese. Most patients enrolled were fibrosis level F0 or F1 (median 76% per treatment group). The primary outcome in all trials was SVR 12.

Interpretation of Results

Efficacy

The percentage of patients who achieved an SVR 12 was generally high across treatment groups and ranged from 88.6% to 99.7% among those who received GP for 8, 12, or 16 weeks.

Among studies that enrolled non-cirrhotic patients, 90.9% to 99.7% of patients achieved SVR 12 and the response rates were similar among those who received GP for 8 weeks (93.1% to 99.1%) or 12 weeks (90.9% to 99.7%). These studies included patients with all genotypes who were either treatment-naive or had prior IFN- or sofosbuvir/ribavirin-based treatment. Of note, the GP treatment duration for some patient groups was not consistent with the Health Canada recommendations. That is, the non-cirrhotic patients in the 12-week GP groups in ENDURANCE-1, -2, -3, and -4 (total N = 905), and in EXPEDITION-4 (N = 84 ESRD), received treatment for longer than recommended in the product monograph. These patients made up the majority of non-cirrhotic patients enrolled in the trials. Data from two trials (ENDURANCE-1 and -3), suggest that GP 8 weeks is noninferior to GP 12 weeks in non-cirrhotic genotype 1 and 3 patients. However, ENDURANCE-3 did not randomly assign patients to the GP 8-week group; thus, these data should be interpreted with caution as there may be differences in measured and unmeasured confounders between the 12-week and 8-week groups.

Two trials (SURVEYOR-II Part 3 and EXPEDITION-1) enrolled only patients with compensated cirrhosis and showed an SVR 12 rate ranging from 95.7% to 99.3% among treatment-naive and treatment-experienced patients with genotype 1, 2, 4, 5, or 6 HCV infection. The SVR 12 rate was also high among the cirrhotic and non-cirrhotic patients with ESRD enrolled in the EXPEDITION-4 study (98.1%; 95% CI, 95.4% to 100%). Health Canada has approved GP for use in patients with ESRD, for whom treatment options may be limited. Based on the product monographs, daclatasvir, asunaprevir, and elbasvir/grazoprevir may be used in patients with severe renal impairment, including those with ESRD.[28,33,35] Other pan-genotypic DAA regimens (sofosbuvir/velpatasvir ± voxilaprevir or sofosbuvir/ledipasvir) have not been approved for use in those with severe renal impairment or ESRD.[29,30,36],

Health Canada has approved GP for use in genotype 1 patients who have failed to respond to an NS3/4A protease inhibitor or an NS5A inhibitor, but not both classes of drugs, based on data from the phase II MAGELLAN-1 Part 2 trial. Although genotype 1, 4, 5, and 6 HCV patients were eligible for enrolment in this study, all but four had genotype 1 infection (96%). Overall, the SVR 12 rate was 88.6% (95% CI, 76.0% to 95.0%) in patients who received GP for 12 weeks and 91.5% (95% CI, 80.1% to 96.6%) in those who received 16 weeks of treatment; however, when broken down by treatment history, all NS3/4A inhibitor–experienced patients achieved SVR 12 (100%; total N = 27), and 88% (GP 12 weeks) and 94% (GP 16 weeks) of the NS5A-experienced patients (total N = 34), and 79% (GP 12 weeks) and 81% (GP 16 weeks) of the NS3/4A- and NS5A inhibitor–experienced patients (total N = 30) achieved SVR 12. In the GP 12- and 16-week groups, 32% and 38% of patients, respectively, received the duration of treatment recommended by Health Canada and, although the subgroups were defined a priori, the trial was not designed or powered to test for subgroup effects. As the data in DAA treatment–experienced patients are scarce, additional information may be needed to determine the role of GP in these patients especially in light of the approval of sofosbuvir/velpatasvir/voxilaprevir. This pan-genotypic regimen is currently under review by CDR for patients previously treated with an NS5A inhibitor (genotype 1 to 6), or sofosbuvir without an NS5A inhibitor (genotype 1 to 4).[36]

The key limitation of the available evidence was the lack of head-to-head comparative data, as eight of the 10 trials did not include another DAA-based regimen as a randomized control group. Six of the 10 studies were uncontrolled or assigned some patients to groups non-randomly. Data from ENDURANCE-3 suggest that GP for 12 weeks was noninferior to sofosbuvir/daclatasvir in treatment-naive, non-cirrhotic patients with genotype 3 HCV infection (difference in SVR 12: −1.2%; 95% CI, −5.6% to 3.1%); however, the most relevant comparator, GP 8 weeks versus sofosbuvir/daclatasvir, was not tested. GP for 8 weeks met the noninferiority criteria compared with sofosbuvir/ribavirin 12 weeks (difference in SVR 12: 4.3%; 95% CI, –3.5% to 12.1%) in non-cirrhotic treatment-naive and prior IFN-based treatment-experienced Japanese patients with genotype 2 HCV infection (CERTAIN-2), but this trial used a 10% noninferiority margin, which may be considered overly broad. Moreover, there was no evaluation of noninferiority using the per-protocol population. The per-protocol analysis may be considered a more methodologically robust and conservative estimate, and concordance between the ITT and per-protocol analysis is needed to determine noninferiority. The external validity may be limited, given that the study enrolled Japanese patients only, used a lower ribavirin dose than is used in Canada, and included an active control that may be considered suboptimal based on current treatment standards.[3,4] Importantly, there were no data comparing GP to the other pan-genotypic DAA regimens that are commonly used in Canada (e.g., sofosbuvir/velpatasvir [Epclusa] or

sofosbuvir/ledipasvir [Harvoni]), although this may not have been feasible given the rapid pace of development of treatments for hepatitis C.

All but one of the studies were open-label, and awareness of treatment allocation may have influenced subjective measures, such as quality of life and reporting of adverse events. The trials evaluated SVR 12, which is a key outcome; however, none were designed to assess longer-term outcomes, such as hepatic-related morbidity or mortality, which are important to patients. However, there is some observational data suggesting that the risk of hepatocellular carcinoma was reduced after achieving SVR using DAA- or interferon-based treatment.[58,59] All trials, except MAGELLAN-1 Part 2, evaluated patient-reported outcomes as exploratory outcomes. The instruments used included the SF-36 (seven trials), the EQ-5D (nine trials), the FSS (eight trials), and the WPAI-HCV (seven trials). Between-group statistical comparisons were conducted in the ENDURANCE-2, ENDURANCE-3, and CERTAIN-2 studies; however, no statistically significant differences were detected between GP and placebo, sofosbuvir/daclatasvir, or sofosbuvir/ribavirin for the instruments tested. Patient-reported outcomes reported in these and the other trials were difficult to interpret due to limitations in the data, including the open-label design, missing data, analysis methods used (i.e., no imputation of missing data or control of multiplicity), or the lack of a control group.

Among the included studies, data were limited for certain subgroup of patients. In total, 44 non-cirrhotic and 47 cirrhotic treatment-experienced genotype 3 patients were enrolled in SURVEYOR-II Part 3, which was a phase II trial. The GP 12-week group, which had the lowest SVR 12 rate (90.9%, N = 22), received a shorter treatment regimen than recommended by Health Canada (12 versus 16 weeks). The SVR 12 response rate was greater than 95% in treatment-experienced genotype 3 patients who received 16 weeks of GP. Few patients with genotype 5 and 6 were enrolled (N = 31 and 37, respectively), which reflects the low global prevalence of these subtypes.[57] Patients with HIV coinfection or solid-organ transplant were excluded from the trials; however, two supporting studies were found that provided some data. These open-label, uncontrolled studies evaluated the use of GP in patients who had undergone a liver or kidney transplant (MAGELLAN-2, Appendix 6) or those with HIV coinfection (EXPEDITION-2, Appendix 7). The MAGELLAN-2 study enrolled 100 patients (80 liver transplant and 20 kidney transplant recipients) who had genotype 1 to 6 HCV infection and no cirrhosis. Of these patients, 66% were treatment-naive and 34% had previously received IFN- or sofosbuvir/ribavirin-based therapy. Overall 98% (95% CI, [redacted]) of patients who received GP for 12 weeks achieved SVR 12, which met the noninferiority criteria compared with a historical control (sofosbuvir/daclatasvir or sofosbuvir/ ledipasvir), which was relevant based on the current standard of care. Two patients were nonresponders; one was due to missing SVR 12 data and the other was due to relapse. The EXPEDITION-2 study enrolled adults with HCV genotype 1 to 6 and HIV coinfection (N = 153) who were treatment-naive (82%) or treatment-experienced (IFN- or sofosbuvir/ribavirin-based therapy (18%). Patients without cirrhosis (90%) received GP for 8 weeks and those with cirrhosis received 12 weeks of treatment (10%). Of these patients, 94% were on ART. The overall SVR 12 rate was 98% (95% CI, 95.8% to 100%), which met the noninferiority criteria versus a historical control (sofosbuvir/ledipasvir or elbasvir/grazoprevir). Three patients were nonresponders, including one non-cirrhotic patient with missing SVR 12 data, and two cirrhotic patients (on-treatment virologic failure, premature discontinuation of study drug). As with some of the pivotal trials, these studies were limited due to the lack of randomization and comparator groups, small sample sizes, and open-label design. The Canadian product monograph states that the efficacy and safety of GP has not been established in patients with HIV

coinfection or who have undergone a liver transplant.[2] Other DAA regimens have been approved for use in Canada for these populations (e.g., sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, ombitasvir/paritaprevir/ritonavir, and dasabuvir).[28,30,31]

Harms

In general, the majority of patients experienced one or more adverse events with headache, fatigue, and nausea reported most frequently among those who received GP. In the double-blind placebo-controlled trial, 65% and 58% of patients reported adverse events in the GP and placebo groups, respectively (ENDURANCE-2). Overall, 76%, 62%, and 70% of patients in the GP 12-week, GP 8-week, and sofosbuvir/daclatasvir 12-week groups respectively, reported an adverse event in the ENDURANCE-3 RCT. In the CERTAIN-2 RCT, 76% versus 48% of patients reported an adverse event in the sofosbuvir/ribavirin versus GP groups, respectively, with anemia (35% versus 0%) and increased bilirubin (15.2% versus 1.1%) reported more frequently for sofosbuvir/ribavirin-treated patients. The duration of treatment however, was longer for sofosbuvir/ribavirin (12 weeks) than GP (8 weeks), which may account for some differences in frequency.

The frequency of serious adverse events was highest (24%) in patients with ESRD, most of whom were undergoing dialysis, and those in EXPEDITION-1 (7.5%), which only enrolled patients with compensated cirrhosis. Unfortunately, neither of the studies had a control group; thus, it is not possible to determine to what extent the serious adverse events were related to the study drug or to the patients' underlying medical condition. In the other studies, the frequency of serious adverse events among GP-treated patients ranged from 0.8% to 4.6%, and was similar for GP and placebo or daclatasvir/sofosbuvir in ENDURANCE-2 and -3. In total, four deaths occurred among the 2,180 patients who received GP. One death was reported among patients who received sofosbuvir/daclatasvir (total N = 115); no deaths were reported among those who received placebo or sofosbuvir/ribavirin (N = 146). Two deaths were due to cerebral hemorrhage, one was an accidental overdose, and two had an unknown cause. Hepatic-related toxicity or morbidity events were infrequent and generally occurred in patients with more severe liver disease at baseline. Few patients stopped treatment due to adverse events in all treatment groups (0% to 3.8%). Withdrawals were highest in the trial in patients with ESRD (3.8%).

Two supporting studies in patients who had undergone a liver or kidney transplant (MAGELLAN-2, Appendix 6) or those with HIV coinfection (EXPEDITION-2, Appendix 7) showed a similar adverse event profile as the studies included in the systematic review. In MAGELLAN-2, 85% of patients reported an adverse event, including eight with serious adverse events (8%) and one with an adverse event that led to drug discontinuation (1%). In the EXPEDITION-2 study, 61% of patients reported an adverse event, four (3%) experienced a serious adverse event, and one patient (0.7%) stopped treatment due to adverse events.

Of the included trials, only ENDURANCE-2 was double blinded; thus, reporting of adverse events may be influenced by the patient's knowledge of the treatment received. The lack of an active control group in most of the studies is an important limitation to the available safety data, as comparative data are scarce. Moreover, the trials were not designed to assess longer-term safety of GP. All of the trials excluded patients with hepatitis B coinfection; thus, the trials provide no data on the risk of hepatitis B reactivation, which is listed as a warning on the product monograph.[2] GP also has a number of potentially clinically important drug–drug interactions, which may affect the risk of adverse effects or may reduce the therapeutic effect of GP.[2]

Potential Place in Therapy[2]

GP is a ribavirin-free, pan-genotypic regimen that provides overall SVR rates of greater than 95% to 98% in almost all patients with HCV. In the opinion of the clinical expert consulted by CADTH, this regimen showed a similar adverse event profile when compared with placebo.[6]

GP is a pan-genotypic option with an 8-week treatment duration in treatment-naive patients without cirrhosis. This patient group likely accounts for 80% of HCV patients who remain to be treated. As such, it offers the ability to change the treatment paradigm to treating for 8 weeks in the majority of patients who would otherwise require 12 weeks of treatment with most of the other DAA regimens currently available. Cirrhotic patients would require a 12-week course similar to other pan-genotypic regimens, and some treatment-experienced patients may require up to 16 weeks of therapy. All patients with HCV need to be evaluated for fibrosis stage, as patients with cirrhosis require long-term monitoring for hepatocellular carcinoma. Similarly, all health care providers, regardless of their level of experience, should ensure that all their HCV patients are evaluated for fibrosis stage.

GP is eliminated through the biliary-fecal route and, as such, is the only pan-genotypic regimen approved by Health Canada for patients with renal disease with an estimated glomerular filtration rate (eGFR) ≤ 30mL/min., or for patients on dialysis. Other potential differentiating attributes of GP include a different option in the context of drug–drug interactions, which may be important in various clinical settings.

In the treatment of HCV, baseline resistance testing has been suggested by international guidelines, depending on the regimen, genotype, fibrosis level, or if patients are prior-treatment experienced.[3,4] This has been a particular issue with certain genotype 3 patients. At present, baseline resistance testing is not needed for GP, unless re-treating DAA-experienced patients. It is very uncommon for patients to fail the presently reimbursed DAA regimens; however, 3% to 10% may fail the first DAA regimen.[7-9] In this population, it is important to consider the prior DAA regimen and obtain a baseline resistance evaluation to guide re-treatment. These patients should be treated by or in conjunction with centres experienced with this challenging patient profile. GP is approved only for the re-treatment of genotype 1 patients, although those who are NS5A-experienced or have a baseline NS5A resistance-associated variant have a lower SVR. Other DAA re-treatment options would include the recently approved sofosbuvir/velpatasvir/voxilaprevir treatment.

As with other protease inhibitor-containing regimens, GP must not be used in patients with Child-Pugh class B or C cirrhosis, or patients with a MELD (Model for End-Stage Liver Disease) score greater greater than 6.

GP is a welcome addition in HCV therapeutics, providing patients a pan-genotypic option that is highly efficacious, seemingly well tolerated, and easy to utilize. It is hoped with screening, linkage to care, and access to the multiple DAA regimens now available, we will be able to realize in Canada the World Health Organization goal of eliminating HCV by 2030.[10]

[2] This information is based on information provided in draft form by the clinical expert consulted by the CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

Conclusions

GP for 8, 12, or 16 weeks was associated with a high percentage of patients achieving SVR 12, with point estimates that ranged from 90.9% to 99.7% in adults with HCV infection genotype 1 to 6 who were treatment-naive, had previously received IFN- or sofosbuvir/ribavirin-based treatment, or had ESRD. The percentage of DAA treatment–experienced, genotype 1 patients who achieved SVR 12 was 88.6% and 91.5% among those who received GP for 12 or 16 weeks, respectively.

GP for 12 weeks was noninferior to sofosbuvir/daclatasvir in treatment-naive, non-cirrhotic patients with genotype 3 HCV infection, although the relevance of this finding is unclear, given that 8 weeks is the approved duration for GP in this population. GP treatment for 8 weeks was also noninferior to sofosbuvir/ribavirin 12 weeks in non-cirrhotic treatment-naive and prior IFN-based treatment-experienced patients with genotype 2 HCV infection; however, the external validity of these findings may be limited, given that the study enrolled Japanese patients only, used a lower ribavirin dose than is used in Canada, and included an active control that may be considered suboptimal based on current treatment standards. In non-cirrhotic genotype 1 HCV patients (treatment-naive or prior IFN-based therapy), GP 8 weeks was noninferior to GP 12 weeks.

HRQoL, fatigue, and work productivity were evaluated as exploratory outcomes using the following instruments: SF-36, EQ-5D, FSS, and the Work Productivity and Activity Index – Hepatitis C. No conclusions could be drawn from these outcomes due to limitations in the data that included the open-label study design, missing data, the analysis methods used, or lack of a control group. Headache, fatigue, and nausea were the adverse events reported most frequently among those who received GP. None of the trials were designed to assess longer-term outcomes, such as hepatic-related morbidity or mortality, which are important to patients.

The key limitation was the limited comparative data, as eight of the 10 trials did not include another DAA-based regimen as a randomized control group, or the comparator selected (i.e., sofosbuvir/ribavirin) was considered suboptimal according to current clinical guidelines. In particular, there were no comparative data versus sofosbuvir/velpatasvir, another pan-genotypic DAA-based regimen that is approved in Canada and has been reviewed by CDR. Six of the 10 studies included in this review were uncontrolled or assigned some patients to groups non-randomly. More complex patients with important concurrent conditions were excluded from the trials; thus, generalizability of the studies' findings to these patients may be limited. Data were scarce for those with HIV coinfection, liver transplant, genotype 5 and 6 HCV infection, treatment-experienced genotype 3 patients, or those with prior DAA-treatment experience.

Appendix 1: Patient Input Summary

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

1. Brief Description of Patient Group Supplying Input

Four groups submitted patient input for this review.

The Canadian Liver Foundation (CLF) is a national organization committed to reducing the incidence and impact of liver disease for Canadians living with or at risk of liver disease, through research, public and professional education programs, patient support programs, and other fundraising and outreach efforts. The CLF has received unrestricted educational grants from AbbVie Corporation, Astellas Pharma Canada, Boehringer Ingelheim (Canada) Inc., Gilead Sciences Canada Inc., Janssen, Merck Canada, Novartis Pharmaceuticals Canada, and Hoffmann-La Roche.

The Canadian Treatment Action Council (CTAC) is a national non-governmental organization addressing access to treatment, care, and support for people living with HIV and hepatitis C. Full membership is limited to patients living with HIV, including HCV coinfection, or organizations with a substantial HIV mandate. CTAC received unrestricted organizational and educational grants from the following organizations in the 2017-2018 fiscal year: Gilead Sciences and ViiV Healthcare.

The Pacific Hepatitis C Network's mission is to strengthen the capacity of individuals and organizations throughout British Columbia to prevent new hepatitis C virus (HCV) infections and to improve the health and treatment outcomes of people already living with HCV. Its members include individuals who are HCV antibody positive, at risk, or concerned about HCV. The Pacific Hepatitis C Network has received funding from these pharmaceutical companies in the past two years: AbbVie, Bristol-Myers Squibb, Gilead Science, Janssen, and Merck. AbbVie provided information about the glecaprevir/pibrentasvir clinical trial data that was used to complete the submission.

The Hepatitis C Education and Prevention Society (HepCBC) is a non-profit organization run by and for people affected by HCV in British Columbia. They focus on providing peer support, anti-stigma activities, prevention education, and general hepatitis information to the general public, particularly to baby-boomer, Indigenous, and immigrant communities and those living in rural and remote locations. In addition, they encourage testing among at-risk groups. Over the last four years, HepCBC has received funding for hepatitis C–oriented projects (such as publishing educational materials, organizing educational forums, attending and presenting at educational conferences, advertising in newspapers [events and hepatitis C patient awareness], and holding awareness activities) from the following pharmaceutical companies: Merck Pharmaceuticals, Lupin Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, and AbbVie. It has also received support from Rx&D (now Innovative Medicines Canada), the pharmaceutical umbrella organization. The authors of this submission attended conferences and meetings that were funded by the aforementioned pharmaceutical companies.

CLF, CTAC, and HepCBC did not report the role of pharmaceutical companies in the preparation of their submissions.

2. Condition-Related Information

The information was gathered through interviews with patients and caregivers affected by hepatitis C. It was also gathered from patients, caregivers, and health care professionals through surveys, social media, meetings with support groups, informal discussions, and via a webinar that included patients diagnosed with hepatitis C. Information gathered from previous patient input consultations from other hepatitis C drugs was used as well.

Hepatitis C is a serious and potentially life-threatening liver disease that may lead to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), liver failure, and hepatic encephalopathy. Data from Health Canada (2011) suggests that approximately 245,000 Canadians are presently infected with HCV, with as many as 44% of them unaware they are living with the virus. One patient in a patient group stated, "I was unaware that I had hepatitis C until 2009, some 30 years after contracting it." The symptoms of hepatitis C include fatigue, nausea, headaches, sensitivities to light and food, memory loss, mood swings, itchy skin, abdominal pain, severe joint and muscle pain, portal hypertension, sleeplessness, slowed reflexes, psoriasis, peripheral neuropathy, osteopenia, diarrhea, and muscle wasting. Hepatitis C patients also express psychological and emotional stress on them, as well as social isolation. The symptoms may be severe and can limit a patient's ability to work, manage their home, care for family members, and maintain friendships. According to patient groups, it was described as "a disease that can and does affect all aspects of a person's life and that of their family and friends and their colleagues and community." The symptoms and impact of hepatitis C described by patients ranged from asymptomatic to symptoms such as, according to one patient, "insomnia, tiredness, itchiness, poor circulation, constipation and (the) fear of accidently infecting someone else makes day-to-day life difficult…" "Brain fog" was also mentioned. A large proportion of people living with HIV infection are coinfected with HCV. In 2007, the Public Health Agency of Canada estimated that 20% of people living with HIV are coinfected with hepatitis C. The presence of both viruses may exacerbate the progression of liver disease, and many of their respective medications impact one another.

For caregivers (spouses, parents, and adult children), the challenges associated with caring and achieving a cure for hepatitis C patients are significant. They have described that caring for a hepatitis C patient undergoing treatment is a relentless and ongoing task. The symptoms of advanced hepatitis C can leave the patient completely dependent and unable to contribute financially, physically, psychologically, or emotionally to the household, or the relationship. Caregivers must endure their loved one's mood swings, dietary problems, lack of energy and concentration while shouldering the responsibility for managing doctor's appointments and household responsibilities. As the patient's symptoms and behaviour become more difficult to manage, families and marriages can break apart due to stress, financial difficulties, and social isolation.

3. Current Therapy-Related Information

The former standard therapy, which usually involved weekly injections of pegylated interferon accompanied by ribavirin for up to 48 weeks, could be long and grueling. The adverse effects caused by the former standard therapies were severe and debilitating, such as extreme fatigue, depression, nausea, weakness, dry mouth, flu symptoms, lowered platelet count, lowered red blood cell count, changed taste, and hair loss. In recent years, direct-acting antiviral (DAA) treatments became available to treat patients with hepatitis C, bringing with them the advantages of higher efficacy rates and reduced side effects. Several all-oral DAA treatments for HCV have been approved, both federally and

provincially. Interferon-free treatment options for genotype 1 patients include sofosbuvir/ledipasvir (Harvoni) and ombitasvir/paritaprevir/ritonavir plus dasabuvir (Holkira Pak). They offer patients a low pill burden, few side effects, a shorter treatment length (12 weeks) and efficacy rates of 90% or higher. Treatment options for genotypes 2, 3, 4, 5, and 6 have also begun to improve with the advent of the pan-genotypic therapy sofosbuvir/velpatasvir (Epclusa), and targeted therapies for specific patient groups.

In the Pacific Hepatitis C Network, the patients who had prior interferon-based therapy complained about nonresponse, post-treatment relapse, and interferon-related side effects. All of these patients were cured after the use of interferon-free DAAs. Many patients from CTAC expressed optimism about the promising benefits related to the use of DAAs when they were asked about the potential of these medications when DAAs they were beginning to roll out in Canada. The additional benefit of DAAs include: easier to take, fewer pills, no injections, and shorter treatment times. As new DAAs have become available, caregivers have noted that while side effects are not uncommon with newer treatments, they were generally considered milder and more tolerable than those associated with pegylated interferon and ribavirin. A caregiver stated, “When he underwent his third attempt at a cure, all side effects were manageable and so much less than any other regimen, despite his F4 cirrhosis and increasing MELD (Model for End-Stage Liver Disease score) and symptoms ... the dosing regimen was easy to administer and tolerate . . . the first was very difficult, the second try almost led to his death.” Currently, the biggest barrier to treatment with the new DAA combinations is their high cost. Even though it has been shown that the earlier a person gets treated, the more likely the treatment is to be successful and the more quality of life will be attained, most such patients are not permitted to access this treatment unless they have either good insurance plans or are willing to pay for it themselves.

4. Expectations About the Drug Being Reviewed

One of the patient groups was able to obtain feedback from a patient who had taken glecaprevir/pibrentasvir as part of a clinical trial. Information about glecaprevir/pibrentasvir was obtained through consultation with physicians who had treated hepatitis C patients with this drug, or published literature.

According to patient groups, hepatitis C patients, regardless of genotype, are looking for a safe, effective, affordable, and easy-to-take therapy that will cure their hepatitis C. Glecaprevir/pibrentasvir, like sofosbuvir/velpatasvir, is an interferon-free DAA which received Health Canada approval for the treatment of chronic HCV infection in adults for all genotypes on August 16, 2017. Data from clinical trials indicated that it offers a high cure rate across all genotypes (1 to 6) with mild side effects (ache, fatigue, nausea, headache, pruritus, and diarrhea). The recommended dose of glecaprevir/pibrentasvir is three tablets administered once daily for as few as 8 to 12 weeks. In addition, this combination therapy has been shown to be effective for patients with and without cirrhosis and those who are post-transplant or have complicated health conditions, including coinfection with HIV, or who have experienced previous treatment failures. The once-a-day regimen may be associated with improved treatment adherence, a shorter treatment course (8 to 12 weeks compared with previous interferon-based regimens), and improved tolerability.

HepCBC reported input from one patient who was accepted into a clinical trial who suggested that at the end of treatment (three months), she was told she was “officially” cured. The only adverse effect was nausea, and it was manageable. The patient stated, “After I was treated, my energy level went from 30% of normal to 80% of normal. I was able to stay awake for four or five hours at a time and was able to walk to the store and bathe,

etc. It slowly got better and I was able to do so much more." The patient's side effects appeared to be similar to those experienced by other patients on other oral DAA treatments.

CTAC noted that despite the potential of this drug to treat a variety of patients, drug–drug interactions may limit its usefulness. For example, several common HIV medications are contraindicated for use with glecaprevir/pibrentasvir.

HepCBC noted the recent investigation into the possibility of hepatitis B virus (HBV) reactivation among HCV patients taking the new interferon-free DAA treatments. They suggested that all HCV patients, about to embark on an all-oral regime, should have their HBV status confirmed prior to starting treatment. HepCBC also noted that research has indicated a possible recurrence of liver cancer following (third generation) DAA treatment. Hepatocellular carcinoma is a factor that must be considered carefully before a treatment regime is prescribed, at least until more data become available.

CLF stated that "for this treatment to have maximum impact, however, it must be available to all patients who need it and this means that there should be few, if any, eligibility criteria for reimbursement. It is critical that patients and their physicians have access to the best possible treatment options regardless of geographic location, financial status, treatment status, or disease severity." Patients groups support the approval of glecaprevir/pibrentasvir because they believe that it is an effective treatment with high cure rates across all genotypes, even among those who are more difficult to treat, and because it has fewer side effects than previous interferon-based treatments.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 7, 2017
Alerts:	Bi-weekly search updates until November 15, 2017
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
Database(s): **Embase** 1974 to 2017 July 06**, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present Search Strategy:		
#	**Searches**	**Results**
1	(glecaprevir* or ABT-493 or "ABT 493" or ABT493 or 1365970-03-1 or K6BUU8J72P).ti,ab,ot,kf,hw,rn,nm.	101
2	(pibrentasvir* or ABT-530 or "ABT 530" or ABT530 or 1353900-92-1 or 2WU922TK3L).ti,ab,ot,kf,hw,rn,nm.	103
3	1 and 2	90
4	(Maviret* or "ABT-493/ABT-530" or "glecaprevir/pibrentasvir").ti,ab,ot,kf,hw.	32
5	3 or 4	90
6	5 use ppez	8
7	glecaprevir/	49
8	(glecaprevir* or ABT-493 or "ABT 493" or ABT493).ti,ab,ot,kw.	67
9	(pibrentasvir* or ABT-530 or "ABT 530" or ABT530).ti,ab,ot,kw.	70
10	pibrentasvir/	47
11	7 or 8	98
12	9 or 10	98
13	11 and 12	88
14	(Maviret* or "ABT-493/ABT-530" or "glecaprevir/pibrentasvir").ti,ab,ot,kw.	32
15	13 or 14	88
16	15 use oemezd	80
17	6 or 16	88
18	conference abstract.pt.	2609756
19	17 not 18	44
20	remove duplicates from 19	39

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	July 4 – July 6, 2017
Keywords:	Glecaprevir/pibrentasvir, chronic hepatitis C
Limits:	No date or language limits used

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

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

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Kwo PY, Poordad F, Asatryan A, Wang S, Wyles DL, Hassanein T, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1–6 without cirrhosis. J Hepatol. 2017 Apr 13. Poordad F, Felizarta F, Asatryan A, Sulkowski MS, Reindollar RW, Landis CS, et al. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. Hepatology. 2017 Jan 27. Gane E, Poordad F, Wang S, Asatryan A, Kwo PY, Lalezari J, et al. High Efficacy of ABT-493 and ABT-530 Treatment in patients with HCV genotype 1 or 3 infection and compensated cirrhosis. Gastroenterology. 2016 Oct;151(4):651-9. Clinical Study Report: R & D/15/1229. An open-label, multi-centre study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 with and without ribavirin in subjects with chronic hepatitis C virus (HCV) genotype 1, 4, 5, and 6 infection (SURVEYOR-I). [CONFIDENTIAL internal manufacturer's report]. Lake Bluff (IL): AbbVie Inc.; 2016 May 20. MAGELLAN-1 Part 1 Clinical Study Report: R & D/16/0160. A randomized, open-label, multi-centre study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 (or ABT-493/ABT-530) with and without ribavirin in adults with chronic hepatitis C virus (HCV) infection who failed a prior direct-acting antiviral (DAA) agent-containing therapy. [CONFIDENTIAL internal manufacturer's report]. Lake Bluff (IL): AbbVie Inc.; 2016 Nov 30. SURVEYOR-II Part 1 and 2 Clinical Study Report: R & D/15/1230. A randomized, open-label, multi-centre study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 with and without RBV in subjects with chronic hepatitis C virus (HCV) genotypes 2, 3, 4, 5, or 6 infection (SURVEYOR-II). [CONFIDENTIAL internal manufacturer's report]. Lake Bluff (IL): AbbVie Inc.; 2016 Dec 2.	Phase II non-pivotal trial
Clinical Study Report: R & D/16/1456. Multi-centre, open-label study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus (HCV) genotype 1–6 infection and human immunodeficiency virus-1 (HIV-1) coinfection (EXPEDITION-2). [CONFIDENTIAL internal manufacturer's report]. Lake Bluff (IL): AbbVie Inc.; 2017 May 30. Clinical Study Report: R & D/17/0099. A single-group, open-label, multi-centre study to evaluate the safety and efficacy of ABT-493/ABT-530 in adult post-liver or post-renal transplant recipients with chronic hepatitis C virus genotype 1 to 6 infection (MAGELLAN-2) [CONFIDENTIAL internal manufacturer's report]. Lake Bluff (IL): AbbVie Inc.; 2017 Jun 16.	Non-randomized study
Clinical Study Report: R & D/17/0120. A randomized, open-label, multi-centre study to evaluate the efficacy and safety of ABT-493/ABT-530 in Japanese adults with chronic hepatitis C virus infection (CERTAIN-1). [CONFIDENTIAL internal manufacturer's report]. Lake Bluff (IL): AbbVie Inc.; 2017.	Wrong comparator (Part 1); non-randomized study (Part 2)

Appendix 4: Detailed Outcome Data

Table 14: Virologic Stopping Criteria

Criteria	Definition	Study
Virologic stopping criteria	• Confirmed increase from nadir in HCV RNA (defined as two consecutive HCV RNA measurements of > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment or • Confirmed HCV RNA ≥ 100 IU/mL (defined as two consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during treatment.	ENDURANCE-1 ENDURANCE-2 ENDURANCE-3 CERTAIN-2 ENDURANCE-4, EXPEDITION-4, EXPEDITION-1
	• Confirmed increase from nadir in HCV RNA (defined as two consecutive HCV RNA measurements of > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment or • Failure to achieve HCV RNA < LLOQ by week 6 or • Confirmed HCV RNA ≥ LLOQ (defined as two consecutive HCV RNA measurements ≥ LLOQ) after HCV RNA < LLOQ during treatment.	SURVEYOR-II
	• Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment or • Confirmed HCV RNA ≥ LLOQ (defined as two consecutive HCV RNA measurements ≥ LLOQ) after HCV RNA < LLOQ during treatment.	MAGELLAN-1

HCV = hepatitis C virus; LLOQ = lower limit of quantitation; RNA = ribonucleic acid.
Source: Clinical Study Reports.[6,11-18]

Table 15: Analysis Methods

Study/ Outcome	Analysis	Missing Data	Control of Multiplicity	Subgroups of Interest
ENDURANCE-1				
SVR 12	Percentage of patients in group A (12-week GP) achieving SVR 12 and a 2-sided 95% CI was calculated using the normal approximation to the binomial distribution, unless the rate for SVR 12 was 100%, then the Wilson's score method was used for the CI instead. • If lower bound of 95% CI greater than 91% in the ITT-PS population, then 12-week GP noninferior to historical control. • If the lower bound of the CI for the difference was above the NI margin of −5%, then the 8-week regimen was considered noninferior to the 12-week regimen (PP population). • Noninferiority of GP 8 weeks versus 12 weeks based on the ITT-PS population.	Backward imputation for missing data; otherwise, those with missing data counted as failures.	A fixed-sequence testing procedure was used to control inflated type I error rate for the primary efficacy end points.	Genotype 1 subtype, prior treatment, baseline HCV RNA level, estimated glomerular filtration rate, fibrosis stage.

Study/ Outcome	Analysis	Missing Data	Control of Multiplicity	Subgroups of Interest
Relapse and virologic failure	Percentage of patients with a 2-sided 95% Wilson score CI and the difference in rates (group B minus group A) with a 2-sided 95% Wilson score CI, were summarized.	If HCV RNA values from the central laboratory were missing but a local laboratory value was present in the appropriate time period, then the local laboratory value was used to assess post-treatment relapse and on-treatment virologic failure.	None	Subgroups for "relapse": same as for SVR 12.
PRO	Mean change from baseline to final treatment visit and from baseline to post-treatment week 12 were compared between treatment arms using an ANCOVA model, with treatment group as a factor and baseline score as a covariate.	No imputation for missing items in EQ-5D-3L.	None	None
ENDURANCE-2				
SVR 12	Percentage of patients in group A (GP) achieving SVR 12 and a 2-sided 95% CI was calculated using the normal approximation to the binomial distribution, unless the rate for SVR 12 was 100%, then the Wilson's score method was used for the CI instead. If the 2-sided 95% lower confidence bound of the SVR 12 rate within group A was > 89%, then the GP regimen was considered noninferior to the SOF + RBV regimen. The secondary efficacy end point was the superiority of the percentage of group A patients, excluding prior SOF + RBV ± peg-IFN failures, with SVR 12 to the 95% SVR 12 rate of the standard of care (SOF + RBV for 12 weeks). Superior or lower CI was > 95%.	Backward imputation for missing data; otherwise, those with missing data counted as failures.	A fixed-sequence testing procedure was used to control inflated type 1 error rate for the primary efficacy end point and the first secondary efficacy end point (superiority of the SVR 12 rate in group A to the SOF + RBV regimen). Second end point tested only if NI for first was met.	Genotype 2 subtype, prior treatment, baseline HCV RNA level, baseline creatinine clearance, baseline eGFR, fibrosis stage.
Relapse and virologic failure	Percentage of patients with on-treatment virologic failure and post-treatment relapse was presented with 2-sided 95% CIs (group B minus group A) using Wilson's score method. Minimum 77 days of treatment required for relapse analysis.	If HCV RNA values from the central laboratory were missing but a local laboratory value was present in the appropriate time period, then the local laboratory value was used to assess post-treatment relapse and on-treatment virologic failure.	None	Subgroups for "relapses": same as for SVR 12.

Study/ Outcome	Analysis	Missing Data	Control of Multiplicity	Subgroups of Interest
PRO	Mean changes from baseline to final treatment visit were compared between treatment arms using an ANCOVA model, with treatment group as a factor and baseline score as a covariate; the mean changes from baseline to post-treatment week 12 were summarized descriptively for group A.	**SF-36 v2:** the missing items were imputed with the average score of the answered items when ≥ 50% of the items were answered; if respondent did not answer ≥ 50% of the items, the score for that domain was considered missing. **FSS:** the missing items were imputed with the average score of the answered items as long as > 50% of the items were answered. **EQ-5D-3L:** no imputation. **WPAI-HCV score:** no imputation.	None	None
ENDURANCE-3				
SVR 12	Percentage of patients achieving SVR 12 was calculated for each group. Two-sided CIs for the SVR 12 rates of group A (GP for 12 weeks) and group B (SOF + DCV for 12 weeks) and for the difference in SVR 12 rates (group A minus group B) were calculated using the normal approximation to the binomial distribution. The first primary end point was NI of group A to group B, and it was to be demonstrated if the lower bound of the CI for the difference between rates was above the NI margin of −6%, or if the lower bound of the CI for the SVR 12 rate within group A was > 92%, based on the ITT population. • Same NI criteria were used for the comparison of GP 8 weeks versus GP 12 weeks (ITT). • Analyses were repeated with the PP population. • Superiority of group A versus group B was tested if noninferiority was met. Group A was superior if the lower bound of the 95% CI was greater than 0%.	A backward imputation method was used to impute missing responses for SVR analyses.	The Hochberg procedure was used to control for multiplicity for the first primary efficacy objective. If the first primary efficacy objective was achieved, then the second primary efficacy objective (NI in the SVR 12 rate of group C to group A) was tested. If both primary efficacy objectives were achieved, then the first secondary efficacy end point was tested.	Genotype 3 subtype, baseline HCV RNA level, baseline creatinine clearance, baseline eGFR, fibrosis stage.

Study/ Outcome	Analysis	Missing Data	Control of Multiplicity	Subgroups of Interest
Relapse and virologic failure	Percentage of patients with on-treatment virologic failure and post-treatment relapse were presented with 2-sided 95% CIs (group A minus group B, group C minus group A) using Wilson's score method.	If HCV RNA values from the central laboratory were missing but a local laboratory value was present in the appropriate time period, then the local laboratory value was used to assess post-treatment relapse and on-treatment virologic failure.	None	Subgroups for "relapse": same as for SVR 12.
PRO	SF-36v2 (PCS and MCS), FSS total score, EQ-5D-3L health index score and VAS score: mean change from baseline to final treatment visit and from baseline to post-treatment week 12 was compared between treatment arms using an ANCOVA model with treatment group as a factor and baseline score as a covariate.	SF-36v2 scores and FSS total score: the missing items of the FSS questionnaire were imputed with the average score of the answered items as long as more than 50% of the items on the FSS were answered. EQ-5D-3L scores: no imputation for missing items.	None	None
CERTAIN-2				
SVR 12	Percentage of patients achieving SVR 12 was calculated for each group and a 2-sided 95% CI for the difference in SVR 12 rates (group A minus group B) was calculated using the normal approximation to the binomial distribution (ITT population). If the lower bound of the CI for the difference was above the NI margin of –10%, then the 8-week regimen was considered noninferior to the 12-week regimen (SOF + RBV).	A backward imputation method was used to impute missing responses for SVR analyses.	No adjustment of multiplicity.	Genotype 2 subtype, prior treatment, baseline HCV RNA level, baseline creatinine clearance, baseline eGFR, fibrosis stage.
Relapse and virologic failure	Two-sided 95% CIs (Wilson score method) were provided for rates within treatment arms and for the difference between arms (group A minus group B).	No imputation.	None	None
PRO	FSS total score, EQ-5D-3L health index score and VAS score: mean change from baseline to final treatment visit and from baseline to post-treatment week 12 was compared between treatment arms using an ANCOVA model with treatment group as a factor and baseline score as a covariate.	For EQ-5D-3L index and VAS scores, no imputation was performed for missing items. The missing items of the FSS questionnaire were imputed with the average score of the answered items as long as more than 50% of the items on the FSS were answered.	None	None

Study/ Outcome	Analysis	Missing Data	Control of Multiplicity	Subgroups of Interest
ENDURANCE-4				
SVR 12	Number and percentage of patients with SVR 12 (ITT population) summarized with 2-sided 95% CI using the normal approximation to the binomial distribution. If the SVR 12 was 100%, the Wilson's score method was used to calculate CI.	Backward imputation for missing data; otherwise those with missing data counted as failures.	None	Genotype, prior treatment, HCV RNA levels.
Relapse and virologic failure	Wilson's score method to calculate 2-sided 95% CI.	Use local lab data if central lab data missing.	None	Same as above for "relapse."
PRO	Descriptive reporting of change from baseline data; responder analysis (proportion of patients with increase of 2.5 points in the SF-36 MCS and PCS; 5 points in the SF-36 domain scores; or 0.7 in the FSS total score	Same as ENDURANCE-2, except WPAI (rules to handle missing responses outlined in SAP).	None	None
MAGELLAN-1				
SVR 12 relapse virologic failure	Number and percentage of patients with outcome (ITT population) summarized with 95% CI using Wilson score interval.	Same as ENDURANCE-4.	None	Genotype subtype, prior DAA therapy, baseline HCV RNA level.
SURVEYOR-II Part 3 and 4				
SVR 12	• Number and percentage of patients with SVR 12 (ITT population) summarized with 2-sided 95% CI using Wilson score intervals. • Part 4: Cohort of genotype 2 DAA-naive patients without cirrhosis compared with historical cohort with 95% response rate based on SOF + RBV 12 weeks: GP noninferior if lower confidence limit > 89% (based on 2-sided 95% CI using normal approximation).	NR	None	Genotype, prior HCV therapy, baseline HCV RNA level.
Relapse and virologic failure	95% Wilson score intervals.	Same as ENDURANCE-4.	None	Same as above for "relapse."
PRO	Same as ENDURANCE-4.	Same as ENDURANCE-4.	None	None
EXPEDITION-1				
SVR 12	Number and percentage of patients with SVR 12 (ITT population) summarized with 2-sided 95% CI using the normal approximation to the binomial distribution. If the SVR 12 was 100%, the Wilson's score method was used to calculate CI.	Backward imputation for missing data; otherwise, those with missing data counted as failures.	None	HCV genotype and subtype, prior HCV treatment, baseline HCV RNA level.
Relapse and virologic failure	Wilson's score method to calculate 2-sided 95% CI.	As per ENDURANCE-4.	None	Same as above for "relapse."
PRO	As per ENDURANCE-4.	As per ENDURANCE-4.	None	None

Study/ Outcome	Analysis	Missing Data	Control of Multiplicity	Subgroups of Interest
EXPEDITION-4				
SVR 12	Number and percentage of patients with SVR 12 (ITT population) summarized with 2-sided 95% CI using the normal approximation to the binomial distribution. If the SVR 12 was 100%, the Wilson's score method was used to calculate CI (same as ENDURANCE-4).	Backward imputation for missing data; otherwise those with missing data counted as failures.	None (NA)	CKD stage, presence or absence of cirrhosis, genotype subtype, prior HCV treatment, baseline HCV RNA level.
Relapse and virologic failure	Wilson's score method to calculate 2-sided 95% CI.	As per ENDURANCE-4.	None	Same as above for "relapse."
PRO	As per ENDURANCE-4, except no WPAI-HCV.	As per ENDURANCE-4.	None	None

ANCOVA = analysis of covariance; CI = confidence interval; CKD = chronic kidney disease; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; FSS = Fatigue Severity Scale; GP = glecaprevir/pibrentasvir; HCV = hepatitis C virus; HOMA-IR = homeostatic model of assessment for insulin resistance; ITT = intention to treat; ITT-PS = intention-to-treat primary subset; MCS = mental component summary; NA = not applicable; NI = noninferiority; NR = not reported; peg-IFN = pegylated interferon; PCS = physical component summary; PP = per-protocol; PRO = patient-reported outcome; RBV = ribavirin; RNA = ribonucleic acid; SAP = statistical analysis plan; SF-36v2 = Short Form (36) Health Survey, version 2; SOF = sofosbuvir; SVR 12 = sustained virologic response at 12 weeks; VAS = visual analogue scale; WPAI-HCV = Work Productivity and Activity Index – Hepatitis C.
Source: Clinical Study Reports.[6,11-18]

Table 16: Determination of Sample Size / Power Calculations

Study	
ENDURANCE-1	Planned to enroll approximately 620 patients, where at least 270 patients in each of the two treatment arms would be mono-infected HCV genotype 1 DAA–naive for the primary efficacy analysis. With 270 patients in the 12-week group (group A) for the primary efficacy analysis, and assuming that 97% of the patients in group A achieve SVR 12, this study had > 90% power to demonstrate noninferiority of the 12-week treatment group compared with the historical control SVR 12 rate. The study also had > 90% power to demonstrate noninferiority of the 8-week versus 12-week regimen based on a −5% noninferiority margin.
ENDURANCE-2	Planned to enroll 291 to 321 patients, in a 2:1 ratio to the GP group or placebo. The 21 to 51 patients (14 to 34 patients in group A) with prior SOF + RBV ± peg-IFN failure were not to be included in the primary end point; therefore, 180 patients were to be available in group A for the primary end point (SVR 12). With a sample size of 180 patients and assuming that 96% of the patients in group A would achieve SVR 12, this study would have > 90% power to show noninferiority to a current standard-of-care regimen in patients with genotype 2 infection (SOF + RBV for 12 weeks) with a two-sided lower CI greater than 89%.
ENDURANCE-3	Planned to enroll 460 patients, with 230 in group A, 115 in group B and 115 in group C. With a sample size of 230 patients in the 12-week group (group A) and 115 patients in the active control group (group B), this study had 90% power to show noninferiority to a current standard-of-care regimen for HCV genotype 3 (SOF + DCV for 12 weeks) with a lower confidence bound for the within-group A SVR 12 rate > 92% or with a lower confidence bound for the between-group difference (group A – group B) in SVR 12 rates > –6% (assuming the SVR 12 rate was 97% in both arms). With a sample size of 115 patients in group C, the study had approximately 80% power to demonstrate noninferiority of the 8-week duration, with the same underlying assumptions. The 92% threshold was established by applying the 6% noninferiority margin to the SVR rate in the ALLY-3 trial, which showed an SVR 12 rate of 97.6% (80 out of 82) in treatment-naive genotype 3 patients without cirrhosis.
ENDURANCE-4	Planned enrolment: 130 patients. No formal hypothesis tested; thus, no power calculation. If the SVR rate was 97% among 130 patients, the two-sided 95% normal approximation interval would be 94.0% to 99.9%.
EXPEDITION-1	Planned enrolment: 175 patients. No formal hypothesis tested; thus, no power calculation. If the SVR rate was 96% among 175 patients, the two-sided 95% normal approximation interval would be 93.1% to 98.9%.

Study	
EXPEDITION-4	Planned enrolment: 100 patients. No formal hypothesis tested; thus, no power calculation If the SVR rate was 95% among 100 patients, the two-sided 95% normal approximation interval would be (90.7% to 99.3%).
SURVEYOR-II	Planned enrolment: 200 patients for Part 3 and 160 patients for Part 4. If the SVR 12 rate was 96%, then 25 patients per group would result in a two-sided 95% CI of 80% to 99%, and 50 patients would have 95% CI of 87% to 99% using the Wilson score method. In Part 4, with a sample size of 90 genotype 2–infected DAA-naive patients without cirrhosis and assuming that 97% of these patients would achieve SVR 12, there would be greater than 80% power to show noninferiority to the current standard-of-care regimen (SOF + RBV for 12 weeks) with a two-sided 95% lower confidence limit greater than 89% using a 1-sample test for superiority.
MAGELLAN-1	Planned enrolment: 80 patients. If the SVR 12 rate was 95%, 40 patients per group in Part 2 would result in a two-sided 95% CI of 83% to 99% using the Wilson score method.
CERTAIN-2	Planned enrolment: 120 patients. With 80 patients in the GP 8-week group (group A) and 40 patients in the SOF + RBV 12-week group (group B), and assuming that 96% of the patients in group A and 95% of the patients in group B achieve SVR 12, this study had > 80% power to demonstrate noninferiority of the GP 8-week treatment group compared with the SOF + RBV 12-week group in SVR 12 rate (i.e., a two-sided 95% lower confidence bound for the difference above the noninferiority margin of –10%).

CI = confidence interval; DAA = direct-acting antiviral; GP = glecaprevir/pibrentasvir; HCV = hepatitis C virus; ITT = intention to treat; peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR 12 = sustained virologic response at 12 weeks.
Source: Clinical Study Reports.[6,11-18]

Table 17: Virologic Response, Including Subgroups

	ENDURANCE-1		ENDURANCE-2	ENDURANCE-3			CERTAIN-2	
Treatment Group	**GP 12 Weeks (Group A)**	**GP 8 Weeks (Group B)**	**GP 12 Weeks**	**GP 12 Weeks (Group A)**	**SOF/DCV 12 Weeks (Group B)**	**GP 8 Weeks (Group C)**	**GP 8 Weeks**	**SOF + RBV 12 Weeks**
	N = 332[a]	**N = 335[a]**	**N = 196[b]**	**N = 233**	**N = 115**	**N = 157**	**N = 90**	**N = 46**
SVR 12 n/N (%) [95% CI]	331 (99.7) [99.1 to 100]	332 (99.1) [98.1 to 100]	195/196 (99.5) [98.5 to 100.0]	ITT: 222/233 (95.3) [92.6 to 98.0] [redacted]	ITT: 111/115 (96.5) [93.2 to 99.9] [redacted]	ITT: 149/157 (94.9) [91.5 to 98.3] [redacted]	ITT: 88/90 (97.8) [94.7 to 100.0]	ITT: 43/46 (93.5) [86.3 to 100.0]
Between-group difference (95% CI)	GP 12 wks – historical control[c] [redacted] GP 8 wks – GP 12 wks: –0.6% (–1.8 to 0.6%)[d] Historical control[c]: [redacted]		4.7% (2.3% to 7.2%) Historical control 361/381 (94.8%)	GP 12 wks – SOF/DCV: ITT: –1.2% (–5.6 to 3.1%) [redacted] GP 8 wks – GP 12 wks: ITT: –0.4% (–4.8% to 4.0%) [redacted]			4.3 (–3.5 to 12.1)	
Overall virologic failure, n/N (%)	[redacted]	[redacted]	1/196 (0.5)	11/233 (4.7)	4/115 (3.5)	8/157 (5.1)	2/90 (2.2)	3/46 (6.5)
Reason for nonresponse								
On-treatment virologic failure	0	1/335 (0.3)	0	1/233 (0.4)	0	1/157 (0.6)	0	0
Relapse	0	0	0	3/222 (1.4)	1/114 (0.9)	5/150 (3.3)	0	2/45 (4.4)

	ENDURANCE-1		ENDURANCE-2	ENDURANCE-3			CERTAIN-2	
Treatment Group	**GP 12 Weeks (Group A)**	**GP 8 Weeks (Group B)**	**GP 12 Weeks**	**GP 12 Weeks (Group A)**	**SOF/DCV 12 Weeks (Group B)**	**GP 8 Weeks (Group C)**	**GP 8 Weeks**	**SOF + RBV 12 Weeks**
	N = 332[a]	**N = 335[a]**	**N = 196[b]**	**N = 233**	**N = 115**	**N = 157**	**N = 90**	**N = 46**
Premature discontinuation of treatment	0	1/335 (0.3)	0	4/233 (1.7)	1/115 (0.9)	0	1/90 (1.1)	1/46 (2.2)
HCV reinfection	0	0	0	0	0	0	0	0
Missing SVR 12 data	1/332 (0.3)	1/335 (0.3)	1/196 (0.5)	3/233 (1.3)	2/115 (1.7)	2/157 (1.3)	1/90 (1.1)	0
Other	0	0	0	0	0	0	0	0
SVR 12 by Subgroup	N = 352[e]	N = 351[e]						
Genotype n/N (%)								
G 1	[redacted]	[redacted]	3/ 3 (100)	–	–	–	–	–
G 1a	[redacted]	[redacted]						
G 1b	[redacted]	[redacted]						
G 2	–	–	192/193 (99.5)	–	–	–	88/90 (98)	43/46 (93)
G 3	–	–	–	[redacted]	[redacted]	[redacted]	–	–
Fibrosis level, n/N (%)								
F0−F1	[redacted]	[redacted]	149/150 (99)	[redacted]	[redacted]	[redacted]	29/ 29 (100)	14/16 (87.5)
F2	[redacted]	[redacted]	16/ 16 (100)	[redacted]	[redacted]	[redacted]	5/6 (83)	4/4 (100)
F3	[redacted]	[redacted]	30/ 30 (100)	[redacted]	[redacted]	[redacted]	4/4 (100)	1/1 (100)
F4	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]	–	–
Missing	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	50/51 (98)	24/25 (96)
Baseline HCV RNA (IU/mL), n/N (%)								
< 6,000,000	[redacted]	[redacted]	151/152 (99)	[redacted]	[redacted]	[redacted]	80/ 82 (98)	37/ 40 (93)
≥ 6,000,000	[redacted]	[redacted]	44/ 44 (100)	[redacted]	[redacted]	[redacted]	8/8 (100)	6/6 (100)
Treatment history, n/N (%)								
TN	216/217 (99.5)	217/219 (99)	140/141 (99)	222/233 (95)	111/115 (97)	149/157 (95)	73/ 75 (97)	36/ 38 (95)
TE	135/135 (100)	131/132 (99)	55/ 55 (100)	NA	NA	NA	15/ 15 (100)	7/8 (88)
Prior HCV treatment n/N (%)				NA	NA	NA		
SOF/RBV-based	[redacted]	[redacted]	6/6 (100)	–	–	–	–	–
IFN-based	[redacted]	[redacted]	55/ 55 (100)	–	–	–	15/ 15 (100)	7/8 (88)
Renal function (eGFR mL/min/1.73 m^2)								
< 60	[redacted]	[redacted]	1/1 (100)	[redacted]	[redacted]	[redacted]	9/9 (100)	2/2 (100)
60 to < 90	[redacted]	[redacted]	102/103 (99)	[redacted]	[redacted]	[redacted]	59/ 61 (97)	33/ 35 (94)
≥ 90	[redacted]	[redacted]	92/ 92 (100)	[redacted]	[redacted]	[redacted]	20/20 (100)	8/9 (89)
Missing	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]		

	ENDURANCE-1		ENDURANCE-2	ENDURANCE-3			CERTAIN-2	
Treatment Group	**GP 12 Weeks (Group A)**	**GP 8 Weeks (Group B)**	**GP 12 Weeks**	**GP 12 Weeks (Group A)**	**SOF/DCV 12 Weeks (Group B)**	**GP 8 Weeks (Group C)**	**GP 8 Weeks**	**SOF + RBV 12 Weeks**
	N = 332[a]	**N = 335[a]**	**N = 196[b]**	**N = 233**	**N = 115**	**N = 157**	**N = 90**	**N = 46**
HIV coinfection			NA	[redacted]	[redacted]	[redacted]	NA	NA
No	[redacted]	[redacted]	–	–	–	–	–	–
Yes	[redacted]	[redacted]	–	–	–	–	–	–

Table 17: Virologic Response, Including Subgroups (Continued)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4	MAGELLAN-1 Part 2	
Treatment Group	**GP12 Weeks N = 121**	**GP12 Weeks N = 146**	**GP12 Weeks N = 104**	**GP12 Weeks N = 44**	**GP16 Weeks N = 47**
SVR 12 N (%) [95% CI]	120 (99.2) [97.6 to 100.0]	145 (99.3) [98.0 to 100.0]	102 (98.1) [95.4 to 100.0]	39 (88.6) [76.0 to 95.0]	43 (91.5) [80.1 to 96.6]
P value	NA				
Overall virologic failure, n/N (%)	1/121 (0.8)	1/146 (0.7)	2/104 (1.9)	5/44 (11.4)	4/47 (8.5)
Reason for nonresponse					
On-treatment virologic failure	0	0	0	1/44 (2.3)	4/47 (8.5)
Relapse	0/118	1/144 (0.7)	0/100	4/43 (9.3)	0
Discontinued treatment	1/121 (0.8)	0	1/104 (1.0)	0	0
HCV reinfection	0	0	0	0	0
Missing SVR 12 data	0	0	1/104 (1.0)	0	0
Other	0	0	0	0	0
SVR 12 by subgroup					
Genotype n/N (%)					
G 1		89/90 (99)	53/55 (96)	38/43 (88)	40/44 (910
G 1a		49/50 (98)		31/35 (89)	28/32 (88)
G 1b		39/39 (100)		7/8 (88)	10/10 (100)
G 2		31/31 (100)	16/16 (100)		
G 3		–	11/11 (100)		
G 4	75/76 (99)	16/16 (100)	20/20 (100)	1/1 (100)	3/3 (100)
G 5	26/26 (100)	2/2 (100)	1/1 (100)		
G 6	19/19 (100)	7/7 (100)	1/1 (100)		
Cirrhosis, n/N (%) [95% CI]					
Yes	NA	NA	18/20 (90)	14/15 (93)	9/12 (75)
No			84/84 (100)	25/29 (86)	34/35 (97)
Missing					
Fibrosis level, n/N (%) [95% CI]					
F0−F1	103/104 (99)	NR	58/58 (100)	17/20 (85)	28/29 (97)
F2	8/8 (100)		11/11 (100)	2/2 (100)	2/2 (100)
F3	9/9 (100)		17/17 (100)	7/8 (88)	4/4 (100)
F4			15/17 (88)	13/14 (93)	9/12 (75)
Baseline HCV RNA (IU/mL), n/N (%) [95% CI]					
< 6,000,000	98/99 (99)	129/129 (100)	94/96 (98)	35/40 (88)	36/38 (95)
≥ 6,000,000	22/22 (100)	16/17 (94)	8/8 (100)	4/4 (100)	7/9 (78)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4	MAGELLAN-1 Part 2	
Treatment Group	**GP12 Weeks N = 121**	**GP12 Weeks N = 146**	**GP12 Weeks N = 104**	**GP12 Weeks N = 44**	**GP16 Weeks N = 47**
Treatment history, n/N (%) [95% CI]					
TN	82/82 (100)	110/110 (100)	58/60 (97)	NA	NA
TE	38/39 (97)	35/36 (97)	44/44 (100)	39/44 (88.6)	43/47 (91.5)
Prior HCV treatment, n/N (%) [95% CI]					
SOF/RBV-based		11/11 (100)	2/2 (100)		
IFN-based	38/39 (97)	24/25 (96)	42/42 (100)		
PI-experienced / NS5A-naive	–	–	–	14/14 (100)	13/13 (100)
NS5A-experienced ± PI				25/30 (83)	30/34 (88)
NS5A-experienced / PI-experienced	–	–	–	11/14 (79)	13/16 (81)
NS5A-experienced / PI-naive	–	–	–	14/16 (88)	17/18 (94)
Renal function (eGFR mL/min/1.73 m^2)			CKD stage		
< 60	1/1 (100)	7/7 (100)	Stage 4 without dialysis 13/13 (100)	–	1/1 (100)[f]
60 to < 90	48/49 (98)	64/65 (99)	Stage 5 without dialysis 6/6 (100)	6/6 (100)[f]	4/5 (80)[f]
≥ 90	69/69 (100)	74/74 (100)	On dialysis 83/85 (98)	33/38 (87)[f]	38/41 (93)[f]
Missing	2/2 (100)	–	–	–	–

Table 17: Virologic Response Including Subgroups (Continued)

	SURVEYOR-II Part 3				SURVEYOR-II Part 4	
Treatment Group	**GP 12 Weeks**	**GP 16 Weeks**	**GP 12 Weeks**	**GP 16 Weeks**	**GP 8 Weeks**	**GP 8 Weeks**
Population	**G 3 TE No Cirrhosis**	**G 3 TE No Cirrhosis**	**G 3 TN Cirrhosis**	**G 3 TE Cirrhosis**	**G 2 TN, TE No Cirrhosis**	**G 4, 5, 6 TN, TE No Cirrhosis**
Total N	**22**	**22**	**40**	**47**	**145[g]**	**58**
SVR 12 N (%) [95% CI]	20 (90.9) [72.2, 97.5]	21 (95.5) [78.2, 99.2]	39 (97.5) [87.1, 99.6]	45 (95.7) [85.8, 98.8]	142 (97.9) [94.1, 99.3]	54/58 (93.1) [83.6, 97.3]
P value						
Overall virologic failure, n/N (%)	2/22 (9.1)	1/22 (4.5)	1/40 (2.5)	2/47 (4.3)	3/145 (2.1)	4/58 (6.9)
Reason for nonresponse						
On-treatment virologic failure	0	0	0	1/47 (2.1)	0	0
Relapse	2/22 (9.1)	1/22 (4.5)	0	1/46 (2.2)	2/144 (1.4)	0/57
Discontinued treatment	0	0	0	0	1/145 (0.7)	1/58 (1.7)
HCV reinfection	0	0	0	0	0	0
Missing SVR 12 data	0	0	1/40 (2.5)	0	0	3/58 (5.2)
Other	0	0	0	0	0	0
SVR 12 by Subgroup						
Genotype, n/N (%)						
G 1					2/2 (100)	
G 1a						
G 1b						
G 2					140/143 (98)	
G 3	20/22 (90.9)	21/22 (95.5)	39/40 (98)	45/47 (96)		
G 4						43/46 (94)
G 5						2/2 (100)
G 6						9/10 (90)
Cirrhosis, n/N (%) [95% CI]						
Yes	NA	NA	39/40 (98)	45/47 (96)		
No	20/22 (91)	21/22 (95)	NA	NA		
Missing						
Fibrosis level, n/N (%) [95% CI]						
F0−F1	10/11 (91)	14/15 (93)	–	–	119/121 (98)	43/47 (92)
F2	3/ 4 (75)	2/2 (100)	–	–	9/9 (100)	3/3 (100)
F3	7/7 (100)	5/5 (100)	–-	–	12/13 (92)	8/8 (100)
F4	–	–	39/40 (98)	45/47 (96)	–	–
Baseline HCV RNA (IU/mL), n/N (%) [95% CI]						
< 6,000,000	13/13 (100)	15/15 (100)	35/36 (97)	36/37 (97)	80/81 (99)	46/49 (94)
≥ 6,000,000	7/9 (78)	6/7 (86)	4/4 (100)	9/10 (90)	60/62 (97)	8/9 (89)
Treatment history, n/N (%) [95% CI]						
TN	NA	NA	39/40 (98)	NA	126/127 (99)	45/49 (92)
TE	20/22 (91)	21/22 (95)	NA	45/47 (96)	14/16 (88)	9/9 (100)
Prior HCV treatment, n/N (%) [95% CI]						
SOF/RBV-based	8/8 (100)	9/9 (100)	NA	24/25 (96)	5/6 (83)	–
IFN-based	12/14 (86)	12/13 (92)	NA	21/22 (96)	9/10 (90)	9/9 (100)

	SURVEYOR-II Part 3				SURVEYOR-II Part 4	
Treatment Group	**GP 12 Weeks**	**GP 16 Weeks**	**GP 12 Weeks**	**GP 16 Weeks**	**GP 8 Weeks**	**GP 8 Weeks**
Population	**G 3 TE No Cirrhosis**	**G 3 TE No Cirrhosis**	**G 3 TN Cirrhosis**	**G 3 TE Cirrhosis**	**G 2 TN, TE No Cirrhosis**	**G 4, 5, 6 TN, TE No Cirrhosis**
Other						
Renal function, (eGFR mL/min/1.73 m^2)						
< 60	–	1/1 (100)	1/1 (100)	–	6/6 (100)	–
60 to < 90	10/11 (91)	14/15 (93)	16/16 (100)	21/22 (96)	75/76 (99)	20/22 (91)
≥ 90	10/11 (91)	6/6 (100)	19/20 (95)	20/21 (95)	56/58 (97)	33/35 (94)
Missing	–	–	3/3 (100)	4/4 (100)	3/3 (100)	1/1 (100)

CI = confidence interval; CKD = chronic kidney disease; DCV = daclatasvir; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; G = genotype; GP = glecaprevir/pibrentasvir; HCV = hepatitis C virus; IFN – interferon; min = minute; ITT = intention to treat; NA = not applicable; NR = not reported; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PP = per-protocol; RBV = ribavirin; RNA= ribonucleic acid; SOF = sofosbuvir; SVR 12 = sustained virologic response at 12 weeks; TE = treatment-experienced; TN = treatment-naive; wk = week.

[a] ITT-PS population (ITT subset of HCV mono-infected DAA-naive patients), which included 95% of treated patients.

[b] Excluding patients with prior SOF + RBV ± peg-IFN treatment failures (N = 6, 3%).

[c] Historical control was ombitasvir/paritaprevir/ritonavir + dasabuvir ± RBV or SOF/ledipasvir for 12 weeks.

[d] Treatment difference for GP 8 weeks versus GP 12 weeks was 0.0 (95% CI, −1.1 to 1.1) based on the PP, mono-infected and DAA-naive population. GP 8 weeks was noninferior to GP 12 weeks, as the lower limit of the 95% CI was greater than the −5% noninferiority margin.

[e] ITT population, imputation of missing data as failures.

[f] Categories based on creatinine clearance.

[g] SURVEYOR-II Part 4: Two genotype 2–infected patients who were later determined to be infected with genotype 1 were included in the ITT results but excluded from the comparison with the historical control.

Source: Clinical Study Reports.[6,11-18]

Table 18: Short Form (36) Health Survey Results

	ENDURANCE-2		ENDURANCE-3		
	GP 12 Weeks N = 202	**Placebo N = 100**	**GP 12 Weeks (Group A) N = 233**	**SOF/DCV 12 Weeks (Group B) N = 115**	**GP 8 Weeks (Group C) N = 157**
SF-36 physical component score					
Baseline					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final treatment visit					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]		
P value	[redacted]		[redacted]		
Follow-up week 12					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]		
P value	[redacted]		[redacted]		

	ENDURANCE-2		ENDURANCE-3		
	GP 12 Weeks N = 202	Placebo N = 100	GP 12 Weeks (Group A) N = 233	SOF/DCV 12 Weeks (Group B) N = 115	GP 8 Weeks (Group C) N = 157
SF-36 mental component score					
Baseline					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final treatment visit					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]		
P value	[redacted]		[redacted]		
Follow-up week 12					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]		
P value	[redacted]		[redacted]		

Table 18: Short Form (36) Health Survey (Continued)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4	SURVEYOR-II Part 3		SURVEYOR-II Part 4
	GP 12 Weeks N = 121	GP 12 Weeks N = 146[a]	GP 12 Weeks N = 104	GP 12 Weeks[b] N = 62	GP 16 Weeks[b] N = 69	GP 8 Weeks[b] N = 203
SF-36 physical component score						
Baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final treatment visit						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up week 12						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 mental component score						
Baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final treatment visit						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4	SURVEYOR-II Part 3		SURVEYOR-II Part 4
	GP 12 Weeks N = 121	GP 12 Weeks N = 146[a]	GP 12 Weeks N = 104	GP 12 Weeks[b] N = 62	GP 16 Weeks[b] N = 69	GP 8 Weeks[b] N = 203
Follow-up week 12						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DCV = daclatasvir; GP = glecaprevir/pibrentasvir; SD = standard deviation; SF-36 = Short Form (36) Health Survey; GP = glecaprevir/pibrentasvir; SD = standard deviation; SOF = sofosbuvir.

[a] End-of-treatment visit uses last post-treatment data available. Follow-up week 12 includes patients with baseline and week 12 data.

[b] Pooled reported of health-related quality-of-life data based on treatment duration (8, 12, or 16 weeks).

Source: Clinical Study Reports.[6,11-15,17,18]

Table 19: EuroQol 5-Dimensions Questionnaire

	ENDURANCE-1		ENDURANCE-2		ENDURANCE-3			CERTAIN-2	
	GP 12 Weeks N = 352	GP 8 Weeks N = 351	GP 12 Weeks N = 202	Placebo N = 100	GP 12 Weeks (Group A) N = 233	SOF/DCV 12 Weeks (Group B) N = 115	GP 8 Weeks (Group C) N = 157	GP 8 Weeks N = 90	SOF/RBV 12 Weeks N = 46
EQ-5D Index Score									
Baseline									
N	[redacted]								
Mean (SD)	[redacted]								
Final treatment visit									
N	[redacted]								
Mean (SD) change from baseline	[redacted]								
Between-group difference (95% CI)	[redacted]								
P value	[redacted]								
Follow-up week 12									
N	[redacted]								
Mean (SD) change from baseline	[redacted]								
Between-group difference (95% CI)	[redacted]								
P value	[redacted]								
EQ-5D VAS									
Baseline									
N	[redacted]								
Mean (SD)	[redacted]								
Final treatment visit									
N	[redacted]								
Mean (SD) change from baseline	[redacted]								
Between-group difference (95% CI)	[redacted]								
P value	[redacted]								

	ENDURANCE-1		ENDURANCE-2		ENDURANCE-3			CERTAIN-2	
	GP 12 Weeks N = 352	GP 8 Weeks N = 351	GP 12 Weeks N = 202	Placebo N = 100	GP 12 Weeks (Group A) N = 233	SOF/DCV 12 Weeks (Group B) N = 115	GP 8 Weeks (Group C) N = 157	GP 8 Weeks N = 90	SOF/RBV 12 Weeks N = 46
Follow-up week 12									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]		[redacted]			[redacted]	
P value	[redacted]		[redacted]		[redacted]			[redacted]	

Table 19: EuroQol 5-Dimensions Questionnaire (Continued)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4	SURVEYOR-II Part 3		SURVEYOR-II Part 4
	GP 12 Weeks N = 121	GP 12 Weeks N = 146[a]	GP 12 Weeks N = 104	GP 12 Weeks[b] N = 62	GP 16 Weeks[b] N = 69	GP 8 Weeks[b] N = 203
ED-5D Index Score						5L
Baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final treatment visit						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up week 12						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ED-5D VAS						
Baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final treatment visit						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up week 12						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DCV = daclatasvir; EQ-5D = EuroQol 5-Dimensions questionnaire; G = genotype; GP = glecaprevir/pibrentasvir; HCV = hepatitis C virus; IFN = interferon; NR = not reported; RBV = ribavirin; SD = standard deviation; SF-36 = Short Form (36) Health Survey; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive; VAS = visual analogue scale.

[a] End-of-treatment visit uses last post-treatment data available. Follow-up week 12 includes patients with baseline and week 12 data.

[b] Pooled reported of HRQoL data based on treatment duration (8, 12, or 16 weeks).

Source: Clinical Study Reports.[6,11-15,17,18]

Table 20: Other Patient-Reported Outcomes

	ENDURANCE-2		ENDURANCE-3			CERTAIN-2	
	GP 12 Weeks N = 202	Placebo N = 100	GP 12 Weeks (Group A) N = 233	SOF + DCV 12 Weeks (Group B) N = 115	GP 8 Weeks (Group C) N = 157	GP 8 Weeks N = 90	SOF + RBV 12 Weeks N = 46
FSS total score							
Baseline							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final treatment visit							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference (95% CI)	[redacted]		[redacted]			[redacted]	
P value	[redacted]		[redacted]			[redacted]	
Follow-up week 12							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference (95% CI)			[redacted]			[redacted]	
P value			[redacted]			[redacted]	
WPAI-HCV overall work impairment score							
Baseline						NR	NR
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Final treatment visit							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Between-group difference (95% CI)	[redacted]		[redacted]				
P value	[redacted]		[redacted]				
Follow-up week 12							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Between-group difference (95% CI)			[redacted]				
P value			[redacted]				
WPAI-HCV activity impairment score							
Baseline						NR	NR
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Final treatment visit							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Between-group difference (95% CI)	[redacted]		[redacted]				

	ENDURANCE-2		ENDURANCE-3			CERTAIN-2	
	GP 12 Weeks N = 202	Placebo N = 100	GP 12 Weeks (Group A) N = 233	SOF + DCV 12 Weeks (Group B) N = 115	GP 8 Weeks (Group C) N = 157	GP 8 Weeks N = 90	SOF + RBV 12 Weeks N = 46
P value	[redacted]		[redacted]				
Follow-up week 12							
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Between-group difference (95% CI)			[redacted]				
P value			[redacted]				

Table 20: Other Patient-Reported Outcomes (Continued)

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4	SURVEYOR-II Part 3		SURVEYOR-II Part 4
	GP 12 Weeks N = 121	GP 12 Weeks N = 146[a]	GP 12 Weeks N = 104	GP 12 Weeks[b] N = 62	GP 16 Weeks[b] N = 69	GP 8 Weeks[b] N = 203
FSS total score						
Baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final treatment visit						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up week 12						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI-HCV overall work impairment score						
Baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Final treatment visit						
N	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Follow-up week 12						
N	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
WPAI-HCV activity impairment score						
Baseline						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

	ENDURANCE-4	EXPEDITION-1	EXPEDITION-4	SURVEYOR-II Part 3		SURVEYOR-II Part 4
	GP 12 Weeks N = 121	GP 12 Weeks N = 146[a]	GP 12 Weeks N = 104	GP 12 Weeks[b] N = 62	GP 16 Weeks[b] N = 69	GP 8 Weeks[b] N = 203
Final treatment visit						
N	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Follow-up week 12						
N	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

CI = confidence interval; DCV = daclatasvir; EQ-5D = EuroQol 5-Dimensions questionnaire; FSS = Fatigue Severity Score; GP = glecaprevir/pibrentasvir; HCV = hepatitis C virus; NR = not reported; RBV = ribavirin; SD = standard deviation; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive; WPAI-HCV = Work Productivity and Activity Index – Hepatitis C.

[a] End-of-treatment visit uses last post-treatment data available. Follow-up week 12 includes patients with baseline and week 12 data.

[b] Pooled reporting of health-related quality-of-life data based on treatment duration (8, 12, or 16 weeks).

Source: Clinical Study Reports.[6,11-15,17,18]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Short Form (36) Health Survey (SF-36)
- Work Productivity and Activity Impairment – Hepatitis C (WPAI-HCV)
- EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L)
- EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L)
- Fatigue Severity Scale (FSS)

Findings

The above outcome measures are briefly summarized in Table 21.

Table 21: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
SF-36	SF-36 is a generic health-assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life.	Yes	2 to 4 (general use)	Ware et al.[60]
WPAI-HCV	WPAI is an instrument used to measure the impact of a disease on work and on daily activities.	No	Unknown	Reilly et al.[61]
EQ-5D-3L	EQ-5D is a general, non–disease-specific health-related quality-of-life questionnaire.	None in CHC	0.033 to 0.074 (general use)	EuroQol group[45] Sinnott et al.[46]
EQ-5D-5L	EQ-5D is a general, non–disease-specific health-related quality-of-life questionnaire.	Yes	Index score: • summarized mean 0.056 (SD 0.011) • summarized median 0.056 (IQR 0.049 to 0.063) (general use)	Health Quality Council of Alberta 2014[62] McClure et al.[47]
FSS	Generic, unidimensional, psychometric instrument designed to assess the impact of fatigue in past week.	Yes	0.33 to 0.82	Krupp et al.[48] Rosa et al.[50] Kleinman et al.[51]

CHC = chronic hepatitis C; EQ-5D = EuroQol 5-Dimensions questionnaire; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FSS = Fatigue Severity Scale; IQR = interquartile range; MCID = minimal clinically important difference; SD = standard deviation; SF-36 = Short Form (36) Health Survey; WPAI-HCV = Work Productivity and Activity Impairment – Hepatitis C.

Short Form (36) Health Survey

SF-36 is a generic health-assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life (HRQoL). SF-36 consists of eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. SF-36 also provides two component summaries: the physical component summary (SF-36 PCS) and the mental component summary (SF-36 MCS), which are created by aggregating the eight domains. The SF-36 PCS, SF-36 MCS and eight domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. Generally, 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.[60]

A systematic review was conducted to identify and provide information on HRQoL instruments for hepatitis C.[63] The authors identified 32 studies and presented the results by types of clinical anchors (for example, hepatitis C status or liver disease severity anchors), but it was not clear in the publication which instruments contributed to the data. Nonetheless, from the publication, two results attributed to SF-36 could be extracted:

- A total of 15 studies with SF-36 were included that compared HRQoL in patients with compensated hepatitis C seropositivity with healthy controls. All 15 studies provided cross-sectional group mean HRQoL differences stratified by hepatitis C status (the clinical anchor). Patients with hepatitis C scored lower on the various domains compared with healthy patients. The largest impact of the disease was on role physical, role emotional, and general health (Table 22).[63]
- A panel of experts was convened to indirectly estimate the minimal clinically important difference (MCID) in hepatitis C based on existing HRQoL data.[63] The panel consisted of three hepatologists and two HRQoL methodologists with expertise in chronic liver disease. Based on the results of the systematic review, the panel determined that the SF-36 vitality scale captures the HRQoL domain that is most relevant to patients with hepatitis C. Using a modified Delphi technique, the expert panel generated a mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale, with a corresponding effect size of 0.2 (range 0.15 to 0.25).[63] MCIDs were not estimated for other dimensions or for the two component scores. Of note, this study did not use an anchor-based method to generate the MCID, which may be preferred and, as such, it is unclear if the estimates represent values patients would identify as clinically important.[64]

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

Table 22: Hepatitis C Patient Versus Healthy Control-Weighted Mean and Median Cross-Sectional Difference (15 Studies)

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

Source: Spiegel 2005.[63]

Work Productivity and Activity Impairment — Hepatitis C

The WPAI questionnaire is an instrument used to measure the impact of a disease on work and on daily activities. It consists of six questions that focus on the following areas: Q1 = current employment status; Q2 = hours missed due to health problems associated with hepatitis C; Q3 = hours missed due to other reasons; Q4 = hours actually worked; Q5 = degree health has affected productivity while working (using a 0 to 10 visual analogue scale [VAS]); Q6 = degree (VAS) health has affected ability to do other regular unpaid activities.[52,61,65] The questionnaire elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing of work was challenging, and the extent to which the patient was limited at work (work impairment) during the past seven days. The work impairment domain is the sum of impairment in work productivity due to absenteeism (productivity loss due to a health-related absence from work, including personal time off, sick days off work, duration of short- or long-term disability, or worker's compensation days) and impairment due to decreased productivity while at work (reduced performance of productivity while at work due to health reasons, including time not being on a task and decreased work quality and quantity). The activity impairment domain refers to impairment in daily activities other than work. Four main outcomes can be generated from the WPAI and expressed in percentages by multiplying the following scores by 100:

- percentage of work time missed due to health (for those who were currently employed) = $\frac{Q2}{Q2+Q4}$
- percentage of impairment while working due to health (for those who were currently employed and actually worked in the past seven days) = $\frac{Q5}{10}$
- overall work impairment percentage due to health (for those who were currently employed) = $\left(\frac{Q2}{Q2+Q4}\right) + \left(\frac{1-Q2}{Q2+Q4}\right) \times \left(\frac{Q5}{10}\right)$
- activity impairment percentage due to health (for all respondents) = $\frac{Q6}{10}$

For those who missed work and did not actually work in the past seven days, the percentage of overall work impairment due to health will be equal to the percentage of work time missed due to health.The scores are presented as a percentage with lower values indicating better quality of life.[52,65]

One study, available only as an abstract, measured the content validity of WPAI in hepatitis C using cognitive debriefing interviews. A total of seven patients interviewed confirmed that the questionnaire was relevant, understandable, and easy to complete.[66]

Although no information on the validity of WPAI or its MCID in hepatitis C patients was found, the MCID for the WPAI has been reported to be ≥ 7 percentage points in patients suffering from Crohn's disease.[52]

EuroQol 5-Dimensions 3-Levels Questionnaire

The EQ-5D is a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments.[44,45] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions, corresponding with 243 different health states. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[44,45] The second part is a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

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

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score for the 3L version (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores below 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 the 3L version of the scale have ranged from 0.033 to 0.074.[46] The MCID for the EQ-5D-3L among CHC patients remains unknown.

EuroQol 5-Dimensions 5-Levels Questionnaire

EQ-5D is a generic quality-of-life instrument developed by the EuroQol Group. It may be applied to a wide range of health conditions and treatments.[67] As a generic measure of HRQoL that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from a patient perspective. In addition to this purpose, the EQ-5D is used in clinical trials to obtain utility weights for economic models.[62] The EQ-5D 5-Levels version (EQ-5D-5L) was introduced in 2005 based on the earlier 3-Levels version (EQ-5D-3L). It consists of an EQ-5D descriptive system and the EQ VAS. The descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with five levels: a level 1 response represents "no problems," level 2 "slight problems," level 3 "moderate problems," level 4 "severe problems," and level 5 "extreme problems" or "unable to perform," which is the worst response in the dimension. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. In total, there are 3,125 possible unique health states defined by the EQ-5D-5L, with 11111 and 55555 representing the best and worst health states. The numerical values assigned to levels 1 to 5 for each dimension reflect rank order categories of function. In terms of measurement properties, these are

ordinal data; they do not have interval properties and therefore should not be summed or averaged to, for example, produce an individual dimension "score." Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm taking the local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[62] The range of index scores will differ according to the scoring algorithm used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead."

The EQ VAS records the respondent's self-rated health on a vertical, VAS where the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The respondents are asked to mark an X on the point of the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[47,67]

Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121 or 21143
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D-5L has been validated in a diverse patient population in six countries.[67] The validity of the 5L version was compared with the standard version among patients with chronic hepatic diseases (n = 1,088), of which 31.8% had CHC.[68] Overall, compared with the standard version, the 5L version appeared to be more feasible (0.8% of patients who completed the 5L version returned blank questionnaires compared with 8.5% of those who were given the standard version). 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 estimates for the index score in the Canadian population have a summarized mean (standard deviation) of 0.056 (0.011), and a summarized median of 0.056 (interquartile range: 0.049 to 0.063).[47] However, the MCID for the EQ-5D-5L among CHC patients was not assessed.

Fatigue Severity Scale

The FSS is a generic, unidimensional, psychometric instrument designed to assess the impact of fatigue over the past week. The FSS consists of a self-administered questionnaire comprising nine items, each using a seven-point Likert scale.[48,49] Each of the nine FSS items is designed to rate the extent of fatigue symptoms and their impact on patient functioning.[50] Responses can vary from strongly disagree (1) to strongly agree (7).[48,49] Scores should be reported as a total (minimum and maximum scores = 9 and 63, respectively), but are also reported as a mean (minimum and maximum means = 1 or 7, respectively).[48,50,51] Lower scores indicate less effect of fatigue on everyday life. The FSS

also includes a VAS measured as a 100 mm horizontal line that provides a single-item measure of overall fatigue severity.[48,51]

Originally designed and initially validated to measure fatigue in multiple sclerosis and systemic lupus erythematosus,[48] the FSS has been tested for validity and reliability in a number of diseases and conditions including, but not limited to, hepatitis C.[50,51] Psychometric and scaling properties of FSS in hepatitis C patients were assessed in one study using baseline data from three clinical trials involving CHC.[51] This study assessed internal consistency and test–retest reliability. In addition, construct validity was assessed using the SF-36.[51] It was found the FSS has good internal consistency reliability (Cronbach's alpha of 0.947 for the FSS total score).[51] Intra-class coefficients of 0.82 for the FSS total score and 0.80 for the VAS have been reported.[51] Also, the FSS total score and the VAS were significantly correlated with the SF-36 vitality subscale ($r = -0.76$ and $r = -0.76$, respectively).[51]

Another study reported the results of a psychometric analysis conducted to evaluate the adequacy and interpretation of FSS scores as a self-report measure of fatigue for clinical trials in patients with CHC virus infection.[50] This study used data from two double-blind, randomized, placebo-controlled, phase IIb trials evaluating the efficacy and safety of simeprevir plus pegylated interferon plus ribavirin in treatment-naive (PILLAR study, n = 386) and treatment-experienced patients (ASPIRE study, n = 462) with CHC virus infection. Patients completed the FSS and EQ-5D at baseline and at regular intervals throughout both trials.[50] FSS total scores demonstrated good internal consistency reliability in both trials (Cronbach's alpha: 0.95 for PILLAR study; 0.96 for ASPIRE study).[50] Test–retest reliability was evaluated by calculating the intra-class correlation. Intra-class correlation for the PILLAR and ASPIRE studies was 0.74 and 0.86, respectively, which met the established criteria of at least 0.7 for test–retest reliability.[50] Correlation with the EQ-5D "usual activity" domain score and EQ VAS was used to assess concurrent validity. The correlation between the FSS total score and EQ VAS was moderate (PILLAR, $r = -0.63$; ASPIRE, $r = -0.66$).[50] A distributional estimate of the minimal important difference (MID) was determined using the standard error of measurement based on reliability of the FSS questionnaire. Estimates of the MID suggested that an interpretable and meaningful improvement in fatigue occurs when there is an observed group mean change in the FSS total score of between 0.33 and 0.82.[50]

Conclusion

- SF-36, a generic health-assessment questionnaire, has shown good construct validity in hepatitis C patients. A mean MCID of 4.2 points (range 3 to 5) on the SF-36 vitality scale has been reported. MCIDs for other dimensions or for the two component scores of the SF-36 for patients with CHC infection were not found in the literature, but the generally recommended MCID from the instrument developer for the PCS and MCS is 2 to 3 points.
- Limited information was found on the validity of the WPAI questionnaire in hepatitis C; however, the MCID for the WPAI has been reported to be ≥ 7 percentage points in patients suffering from Crohn's disease.
- The generic EQ-5D-3L HRQoL instrument has been widely used, but has not been properly validated in CHC. The MCID for the EQ-5D-3L among CHC patients remains unknown.

- The generic EQ-5D-5L HRQoL instrument has been widely used, but its psychometric properties have not been fully evaluated in CHC. Among patients with chronic hepatic diseases, the EQ-5D-5L version appears to be more feasible, consistent, and has a lower ceiling effect compared with the standard version. The MCID for the EQ-5D-5L among CHC patients remains unknown.
- FSS has good internal consistency reliability and test–retest reliability. It is moderately correlated with the EQ-5D and SF-36 HRQoL instruments. The MCID of FSS total score ranges from 0.33 to 0.82.

Appendix 6: Clinical Trials Not Included in the Systematic Review – MAGELLAN-2 Study

Aim

To summarize the phase III, open-label, single-group, MAGELLAN-2 trial in adult post-liver or post–renal transplant recipients with chronic hepatitis C (CHC) virus genotype 1 to 6 infection.[5] This study was excluded from the systematic review because it was a non-randomized controlled clinical trial and was not considered pivotal by Health Canada.

Study Characteristics

Patients 18 years or older, with CHC genotype 1, 2, 3, 4, 5, or 6 infection and non-cirrhotic, were enrolled in this open-label, single-group non-randomized study. Patients were treatment-naive or hepatitis C virus (HCV) treatment–experienced (had failed prior interferon or pegylated interferon [peg-IFN] ± ribavirin, or sofosbuvir/ribavirin ± peg-IFN therapy), and pre- or post-transplant. Previous HCV treatment must have been completed at least two months prior to screening. Genotype 3 patients had to be HCV treatment-naive. They also had to have received a cadaveric or living-donor liver or kidney at least three months before screening. The liver transplant was required as a consequence of HCV infection.

Patients were excluded if they tested positive for hepatitis B surface antigen (HBsAg) or anti-HIV drugs at screening, had a history of drug or alcohol abuse that could preclude adherence to the protocol, had an active or suspected malignancy, had any cause of post-transplant liver disease other than chronic HCV infection, had a second liver or kidney transplant, had a history of post-transplant complications related to hepatic or renal vasculature, had received any other investigational or commercially available direct-acting anti-HCV drugs other than sofosbuvir (e.g., telaprevir, boceprevir, simeprevir, paritaprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, or dasabuvir).

All patients received 12 weeks of glecaprevir/pibrentasvir (GP) therapy (glecaprevir 300 mg and pibrentasvir 120 mg). The primary outcome was sustained virologic response at 12 weeks (SVR 12), and secondary outcomes included the percentage of patients with on-treatment virologic failure, the percentage of patients with post-treatment relapse, and harms. The study was powered to demonstrate noninferiority to the historical SVR 12 rate of 94% (based on the lower bound of a confidence interval having been above a threshold of 86%) using a one-sample test for superiority. The 86% threshold was established by applying an 8% noninferiority margin to a historical SVR 12 rate of 94%. The historical SVR 12 rate of 94% was based on a meta-analysis of SVR 12 rates across genotypes in the SOLAR-1, SOLAR-2, and ALLY-1 studies (genotype 1: 95%; genotype 3: 91%; genotype 4: 100%; genotype 6: 100%), which results in an estimated SVR rate of 94% for the post-transplant patients who received 12 weeks of sofosbuvir/ledipasvir plus ribavirin or sofosbuvir plus daclatasvir plus ribavirin.

The study was conducted at 27 sites in Australia, Canada, Italy, New Zealand, Spain, Taiwan, UK and US.

Study Participants

A total of 100 patients were enrolled and all patients received at least one dose of the study drug. One patient discontinued the study drug prematurely due to adverse events.

The mean age was 59.19 years. Overall, 80% of patients were liver-transplant recipients and 20% were kidney transplant recipients. The majority of patients (66%) were HCV treatment-naive. None of the patients had cirrhosis, and the majority of patients (80%) were fibrosis stage F0 or F1 at baseline (Table 23).

Table 23: Baseline Characteristics in MAGELLAN-2 (Safety Population)

Treatment Group	GP 12 Weeks	GP 12 Weeks	GP 12 Weeks
Population	**Liver Transplant**	**Kidney Transplant**	**Total**
Total N	**80**	**20**	**100**
Age, mean (SD)	[redacted]	[redacted]	59.19 (7.68)
Male, n (%)	[redacted]	[redacted]	75 (75.0)
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
Multi-race	[redacted]	[redacted]	[redacted]
HCV genotype, n (%)			
Genotype 1	[redacted]	[redacted]	57 (57.0)
Genotype 2	[redacted]	[redacted]	13 (13.0)
Genotype 3	[redacted]	[redacted]	24 (24.0)
Genotype 4	[redacted]	[redacted]	4 (4.0)
Genotype 5	[redacted]	[redacted]	0
Genotype 6	[redacted]	[redacted]	2 (2.0)
Baseline HCV RNA			
Log_{10} IU/mL, mean (SD)	[redacted]	[redacted]	[redacted]
≥ 6,000,000 IU/mL, n (%)	[redacted]	[redacted]	[redacted]
Cirrhosis, n (%)	[redacted]	[redacted]	Excluded
Fibrosis stage, n (%)			
F0−F1	[redacted]	[redacted]	80 (80.0)
F2	[redacted]	[redacted]	6 (6.0)
F3	[redacted]	[redacted]	14 (14.0)
F4	[redacted]	[redacted]	0
Treatment history, n (%)			
Treatment-naive	[redacted]	[redacted]	66 (66.0)
Treatment-experienced	[redacted]	[redacted]	34 (34.0)
Prior HCV therapy, n (%)			
SOF + RBV ± peg-IFN	[redacted]	[redacted]	1 (1.0)
IFN or peg-IFN ± RBV	[redacted]	[redacted]	32 (32.0)
Other	[redacted]	[redacted]	1 (1.0)

Treatment Group	GP 12 Weeks	GP 12 Weeks	GP 12 Weeks
Population	**Liver Transplant**	**Kidney Transplant**	**Total**
Prior treatment response, n (%)			
Nonresponder/breakthrough	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]
Unknown/other	[redacted]	[redacted]	[redacted]
Occurrence of prior HCV treatment relative to transplant			
Pre-transplant	[redacted]	[redacted]	24 (24.0)
Post-transplant	[redacted]	[redacted]	10 (10.0)
Baseline eGFR (mL/min/1.73 m^2)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	28.70, 132.20
HIV coinfection, n (%)	[redacted]	[redacted]	excluded

DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; GP = glecaprevir/pibrentasvir; IFN = interferon; peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SD = standard deviation; SOF = sofosbuvir.
Source: Clinical Study Reports.[5]

Efficacy Results

Out of 100 total patients, 98 achieved SVR 12 (98.0%; 95% confidence interval [CI], [redacted]) (Table 24). The noninferiority of GP based on the intention-to-treat (ITT) population was demonstrated as the 95% lower confidence bound for SVR 12 being higher than 86%; hence, SVR 12 for GP met the noninferiority criteria. Two patients were classified as nonresponders: one because of missing SVR 12 data and the other due to relapse by post-treatment week 12.

Safety Results

The majority of patients (85%) experienced at least one adverse event (Table 24). [redacted] patients, [redacted], experienced grade 3 or higher adverse events ([redacted]) assessed as related to the study drug; the events of [redacted] were serious. There were no direct-acting antiviral (DAA)–related serious adverse events in the renal-transplant population. One patient experienced a serious adverse event of cerebrovascular accident on day 50, which led to premature discontinuation of the study drug (last dose of the study drug was on day 49); however, the event was not considered related to the study drug. The most frequently reported adverse events (≥ 10.0% of patients overall) were fatigue, headache, nausea, pruritus, and diarrhea. Among the patients with renal transplantation, fatigue, nausea, and upper respiratory tract infection were the most common adverse events.

Table 24: Summary of Outcomes for MAGELLAN-2 Study

Treatment Group	GP 12 Weeks
Population	**All Patients**
Total N	**100**
SVR 12 (ITT population) N (%) [95% CI][a]	98 (98.0) [redacted]
Nonresponders	2/100 (2.0)
Overall virologic failure, n/N (%)	1/100 (1.0)
Reason for nonresponse	
On-treatment virologic failure	0
Relapse by post-treatment week 12	1/99 (1.0)
Missing SVR 12 data	1/100 (1.0)
Adverse events	
Any adverse events	85 (85.0)
Any serious adverse events	8 (8.0)
Any DAA-related serious adverse event	2 (2.0)
Adverse events leading to drug discontinuation	1 (1.0)
Death	0

CI = confidence interval; DAA = direct-acting antiviral; GP = glecaprevir/pibrentasvir; ITT = intention to treat; SVR 12 = sustained virologic response at 12 weeks.
[a] Calculated using the normal approximation to the binomial distribution.
Source: Clinical Study Reports.[5]

Conclusion

MAGELLAN-2 study was a phase III study of a 12-week fixed-dose combination regimen of GP, which demonstrated efficacy with a high SVR 12 rate of 98.0% (95% CI: [redacted]) among treatment-naive and -experienced (i.e., interferon or peg-IFN ± ribavirin, or sofosbuvir + ribavirin ± peg-IFN), chronic HCV genotype 1 to 6–infected, post-liver, or renal-transplant patients without cirrhosis. One patient (1%) experienced relapse and there were no on-treatment virologic failures. Adverse events were mostly mild in severity, with the most common being fatigue, headache, nausea, pruritus, and diarrhea. Serious adverse events related to GP were infrequent. There were no discontinuations due to treatment-related adverse events.

The trial was limited by the lack of randomization and comparator groups, small sample size (N = 100), and potential bias in the reporting of adverse events due to the lack of blinding. In addition, SVR 12 for the per-protocol population was not reported. The clinical expert consulted for this review stated that differences of less than 5% to 7% in SVR 12 are considered to be clinically unimportant; however, the chosen noninferiority margin is potentially too high to be considered clinically unimportant. Also, there is no Health Canada indication for GP in post–liver transplant patients, and the duration of treatment in MAGELLAN-2 (12 weeks) is longer than the recommended treatment duration for non-cirrhotic patients (8 weeks).

Appendix 7: Clinical Trials Not Included in the Systematic Review – EXPEDITION-2 Study

Aim

To summarize the phase III, open-label EXPEDITION-2 trial in adults with chronic hepatitis C (CHC) virus genotype 1 to genotype 6 infection and HIV coinfection.[69] This study was excluded from the systematic review because it was a non-randomized controlled clinical trial and it was not considered pivotal by Health Canada.

Study Characteristics

Patients 18 years or older with CHC virus genotype 1, 2, 3, 4, 5, or 6 infection, cirrhotic and non-cirrhotic, were enrolled in this open-label, non-randomized study. Patients were treatment-naive or hepatitis C virus (HCV) treatment–experienced (had failed prior interferon or pegylated interferon [peg-IFN] ± ribavirin, or sofosbuvir + ribavirin ± peg-IFN therapy). Genotype 3 patients had to be HCV treatment-naive. Patients had to test positive for anti-HIV antibodies at screening. Patients had to be naive to treatment with any antiretroviral treatment (ART) regimen or on a stable, qualifying HIV-1 ART regimen for at least eight weeks prior to screening. The HIV-1 ART regimen had to include at least one of the following for cirrhotic and non-cirrhotic patients: raltegravir, dolutegravir, rilpivirine, and elvitegravir/cobicistat. For non-cirrhotic patients, the following regimens were also allowed: darunavir co-administered with ritonavir, darunavir/cobicistat, and lopinavir. In addition to the ART medications, patients (both cirrhotic and non-cirrhotic) could take a nucleoside/nucleotide reverse transcriptase inhibitor (N[t]RTI) backbone.

Patients were excluded if, at screening, they tested positive for hepatitis B surface antigen or HIV-2 antibodies, had a history of drug or alcohol abuse that could preclude adherence to the protocol, had an active or suspected malignancy or history of malignancy in the past five years, had uncontrolled diabetes, had received any other investigational or commercially available direct-acting anti-HCV drugs other than sofosbuvir (e.g., telaprevir, boceprevir, simeprevir, paritaprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, or dasabuvir). Patients were excluded for any cause of liver disease other than chronic HCV infection. They were also excluded if HCV genotyping performed during screening indicated either HCV genotype 3 in a patient with prior HCV treatment experience, or coinfection with more than one HCV genotype. Patients with a clinical history of liver decompensation (including ascites noted on physical exam, hepatic encephalopathy, or esophageal variceal bleeding), patients with hepatocellular carcinoma, and patients with a history of solid-organ transplantation) were also excluded.

Enrolled patients were assigned to either the 8- or 12-week treatment arms based on cirrhotic status; non-cirrhotic patients were treated with GP for 8 weeks and patients with compensated cirrhosis were treated with GP for 12 weeks. The primary outcome was SVR 12, and secondary outcomes included on-treatment virologic failure, post-treatment relapse, and harms. The study was powered to demonstrate noninferiority to the historical SVR 12 rate of 96% (i.e., a two-sided 95% lower confidence bound above 90%) using a one-sample test for superiority. The 90% threshold was established by subtracting a noninferiority margin of 6% from the historical SVR 12 rate (historical rate based on sofosbuvir/ledipasvir for 12 weeks [96%; 321 out of 335] and elbasvir/grazoprevir for 12 weeks [96%; 210 out of 218]).

The study was conducted at 36 sites in Australia, Belarus, France, Germany, Poland, Russia, the UK and the US.

Study Participants

A total of 153 patients were enrolled and all patients received at least one dose of the study drug. Two cirrhotic patients discontinued the study drug prematurely: one due to adverse events, the other due to HCV virologic failure. None of the non-cirrhotic patients discontinued the study drug.

The demographic characteristics of the patients are presented in Table 25. The majority of patients were male (83.7%). Additionally, 79.1% of patients reported as white. The majority of patients (81.7%) were HCV treatment-naive and on a stable HIV-1 ART regimen (94%). The mean age was 45 years. Only 10.5% of patients had cirrhosis, and most patients (78.4%) were fibrosis stage F0 or F1 at baseline.

Table 25: Baseline Characteristics in EXPEDITION-2 (Safety Population)

Treatment Group	GP 8 Weeks	GP 12 Weeks	Total
Population	**Non-Cirrhotic Patients**	**Cirrhotic Patients**	
Total N	**137**	**16**	**153**
Age, mean (SD)	45.00 (10.22)	50.00 (8.36)	45.00 (10.16)
Male, n (%)	113 (82.5)	15 (93.8)	128 (83.7)
Race, n (%)			
White	106 (77.4)	15 (93.8)	121 (79.1)
Black or African American	24 (17.5)	1 (6.3)	25 (16.3)
Asian	6 (4.4)	0	6 (3.9)
Multi-race	1 (0.7)	0	1 (0.7)
HCV genotype, n (%)			
Genotype 1	84 (61.3)	10 (62.5)	94 (61.4)
Genotype 2	12 (8.8)	1 (6.3)	13 (8.5)
Genotype 3	22 (16.1)	4 (25.0)	26 (17.0)
Genotype 4	16 (11.7)	1 (6.3)	17 (11.1)
Genotype 5	0	0	0
Genotype 6	3 (2.2)	0	3 (2.0)
Baseline HCV RNA			
Log_{10} IU/mL, mean (SD)	6.10 (0.71)	6.03 (0.64)	6.09 (0.70)
≥ 6,000,000 IU/mL, n (%)	26 (19.0)	2 (12.5)	28 (18.3)
Cirrhosis, n (%)	0	16 (100)	16 (10.5)
Non-cirrhotic, n (%)	137 (100)	0	137 (89.5)
Fibrosis stage, n (%)			
F0−F1	120 (87.6)	0	120 (78.4)
F2	2 (1.5)	0	2 (1.3)
F3	15 (10.9)	0	15 (9.8)
F4	0	16 (100)	16 (10.5)
Treatment history, n (%)			
Treatment-naive	111 (81.0)	14 (87.5)	125 (81.7)
Treatment-experienced	26 (19.0)	2 (12.5)	28 (18.3)

Treatment Group	GP 8 Weeks	GP 12 Weeks	Total
Population	**Non-Cirrhotic Patients**	**Cirrhotic Patients**	
Prior HCV therapy, n (%)			
SOF + RBV ± peg-IFN	3 (2.2)	0	3 (2.0)
IFN or peg-IFN ± RBV	23 (16.8)	2 (12.5)	25 (16.3)
Prior treatment response, n (%)			
Nonresponder/breakthrough	10 (7.3)	1 (6.3)	11 (7.2)
Relapse	8 (5.8)	1 (6.3)	9 (5.9)
Unknown/other	8 (5.8)	0	8 (5.2)
HIV-1 treatment status, n (%)			
ART-naive	9 (6.6)	0	9 (5.9)
ART-treated	128 (93.4)	16 (100)	144 (94.1)
Baseline eGFR (mL/min/1.73m^2)			
Mean (SD)	86.11 (18.93)	94.02 (30.10)	86.94 (20.40)
Range	40.40, 143.50	47.70, 189.20	40.40, 189.20
Baseline CD4+ T-cell count, mean (SD)	626.60 (285.16)	663.70 (400.99)	630.50 (297.91)

ART = antiretroviral treatment; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; GP = glecaprevir/pibrentasvir; IFN = interferon; peg-IFN = pegylated interferon; min = minute; RBV = ribavirin; RNA = ribonucleic acid; SD = standard deviation; SOF = sofosbuvir.
Source: Clinical Study Report.[69]

Efficacy Results

The overall SVR 12 rate was 98.0% (150 out of 153 patients; 95% confidence interval [CI], 95.8% to 100.0%) (Table 26). The noninferiority of GP based on the intention-to-treat (ITT) population was demonstrated as the 95% lower confidence bound for SVR 12 being above 90%; hence, the SVR 12 for GP met the noninferiority criteria. Three patients were nonresponders, one of them was a non-cirrhotic patient, and the other two were cirrhotic. There was only one virologic failure across the overall ITT population, which occurred in a patient with HCV genotype 3a infection who was cirrhotic and HCV treatment-naive, and who was not compliant with GP dosages. There were no relapses. Of the other two patients who did not achieve SVR 12, one was a non-cirrhotic HCV genotype 3a–infected patient whose SVR 12 data was missing, while the other was a cirrhotic genotype 2a–infected patient who prematurely discontinued the study drug on day 25 due to grade 4 serious adverse events (cerebrovascular accident and cerebral hemorrhage).

Safety Results

Approximately 60% of patients experienced at least one adverse event (Table 26). No patient died during the study. One patient who was cirrhotic prematurely discontinued the study drug on day 25 due to serious adverse events (cerebrovascular accident and cerebral hemorrhage) unrelated to the study drug. Four patients experienced serious adverse events, none of which were considered related to the study drug. The most frequently reported (≥ 10.0% of patients) adverse event was fatigue in non-cirrhotic patients, while no adverse event was reported in more than 10% of cirrhotic patients.

Table 26: Summary of Outcomes for EXPEDITION-2 Study

Treatment Group	GP 8 Weeks	GP 12 Weeks	Overall
Population	**Non-Cirrhotic Patients**	**Cirrhotic Patients**	
Total N	**137**	**16**	**153**
SVR 12 (ITT population) N (%) [95% CI][a]	136 (99.3) (96.0 to 99.9)	14 (87.5) (64.0 to 96.5)	150 (98.0) (95.8 to 100.0)
Nonresponders			3/153 (2.0)
Overall virologic failure, n/N (%)			1/153 (0.7)
Reason for nonresponse			
On-treatment virologic failure			1/153 (0.7)
Relapse by post-treatment week 12			0/151
Missing SVR 12 data			1/153 (0.7)
Premature study drug discontinuation			1/153 (0.7)
Adverse events			
Any adverse events	86 (62.8)	8 (50.0)	94 (61.4)
Any serious adverse events	3 (2.2)	1 (6.3)	4 (2.6)
Any DAA-related serious adverse event	0	0	0
Adverse events leading to drug discontinuation	0	1 (6.3)	1 (0.7)
Death	0	0	0

CI = confidence interval; DAA = direct-acting antiviral; GP = glecaprevir/pibrentasvir; ITT = intention to treat; SVR 12 = sustained virologic response at 12 weeks.
[a] Calculated using the normal approximation to the binomial distribution.
Source: Clinical Study Report.[5]

Conclusion

The EXPEDITION-2 study was a phase III study that evaluated the efficacy and safety of the GP combination regimen for 8 weeks in HCV treatment-naive or prior-treatment experienced (interferon or peg-IFN ± ribavirin, or sofosbuvir + ribavirin ± peg-IFN; with the exception of genotype 3 treatment–experienced) non-cirrhotic patients with chronic HCV genotype 1 to 6 and HIV-1 coinfection, and for 12 weeks in patients with compensated cirrhosis. For patients coinfected with HCV and HIV-1, treatment with GP for 8 or 12 weeks was well tolerated and demonstrated efficacy, with a high SVR 12 rate of 98.0% (95% CI: 95.8% to 100.0%), thus establishing that GP was noninferior to both sofosbuvir/ledipasvir and elbasvir/grazoprevir for 12 weeks. Only one patient experienced an on-treatment virologic failure. The patient was genotype 3a–infected and treatment-naive, and had compensated cirrhosis; this patient was not compliant with the GP dosages beyond week 8. No relapses were observed during the study after 8 or 12 weeks of treatment with GP. Adverse events were mostly mild in severity. There were no study drug–related serious adverse events, no discontinuations due to drug-related adverse events, and occurrences of significant laboratory abnormalities were infrequent.

The trial was limited by the lack of randomization and comparator groups, small sample size (N = 153), and potential bias in the reporting of adverse events due to the lack of blinding. In addition, SVR 12 for the per-protocol (PP) population was not reported, although analyses of noninferiority trials using both the ITT and PP populations are recommended, and a trial is considered positive if both ITT and PP analyses support noninferiority.

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