Research Article
Viral Hepatitis

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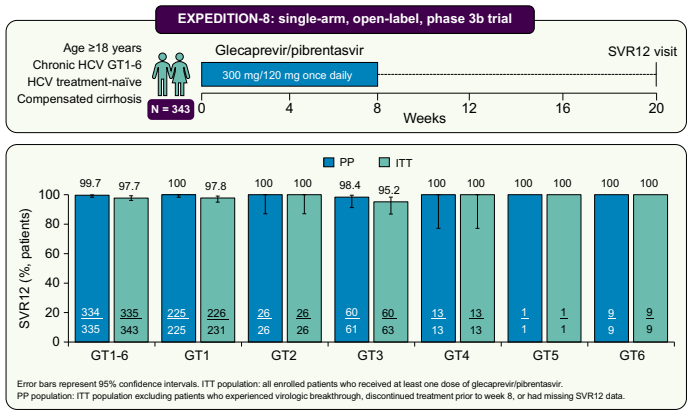
Glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1–6 and compensated cirrhosis: The EXPEDITION-8 trial

Graphical abstract



Highlights

- 343 treatment-naïve patients with chronic HCV genotypes 1–6 and compensated cirrhosis.
- Glecaprevir/pibrentasvir for 8 weeks achieved 99.7% virologic cure.
- One patient experienced relapse at post-treatment week 4.
- Efficacy did not depend on any pre-treatment patient or viral characteristics.
- No drug-related serious adverse events or discontinuations due to adverse events occurred.

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Lay summary

This study was the first to evaluate an 8-week direct-acting antiviral (DAA) regimen active against all major types of hepatitis C virus (HCV) in untreated patients with compensated cirrhosis. High virological cure rates were achieved with glecaprevir/pibrentasvir across HCV genotypes 1–6, and these high cure rates did not depend on any patient or viral characteristics present before treatment. This may simplify care and allow non-specialist healthcare professionals to treat these patients, contributing to global efforts to eliminate HCV.

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Glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1–6 and compensated cirrhosis: The EXPEDITION-8 trial

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Background & Aims: Eight-week glecaprevir/pibrentasvir leads to high rates of sustained virological response at post-treatment week 12 (SVR12) across HCV genotypes (GT) 1–6 in treatment-naïve patients without cirrhosis. We evaluated glecaprevir/pibrentasvir once daily for 8 weeks in treatment-naïve patients with compensated cirrhosis.

Methods: EXPEDITION-8 was a single-arm, multicenter, phase IIIb trial. The primary and key secondary efficacy analyses were to compare the lower bound of the 95% CI of the SVR12 rate in i) patients with GT1,2,4–6 in the per protocol (PP) population, ii) patients with GT1,2,4–6 in the intention-to-treat (ITT) population, iii) patients with GT1–6 in the PP population, and iv) patients with GT1–6 in the ITT population, to pre-defined efficacy thresholds based on historical SVR12 rates for 12 weeks of glecaprevir/pibrentasvir in the same populations. Safety was also assessed.

Results: A total of 343 patients were enrolled. Most patients were male (63%), white (83%), and had GT1 (67%). The SVR12 rate in patients with GT1–6 was 99.7% (n/N = 334/335; 95% CI 98.3–99.9) in the PP population and 97.7% (n/N = 335/343; 95% CI 96.1–99.3) in the ITT population. All primary and key secondary efficacy analyses were achieved. One patient (GT3a) experienced relapse (0.3%) at post-treatment week 4. Common adverse events (≥5%) were fatigue (9%), pruritus (8%), headache (8%), and nausea (6%). Serious adverse events (none related) occurred in 2% of patients. No adverse event led to study drug discontinuation. Clinically significant laboratory abnormalities were infrequent.

Conclusions: Eight-week glecaprevir/pibrentasvir was well tolerated and led to a similarly high SVR12 rate as the 12-week regimen in treatment-naïve patients with chronic HCV GT1–6 infection and compensated cirrhosis.

Trial registration: ClinicalTrials.gov, NCT03089944.

Lay summary: This study was the first to evaluate an 8-week direct-acting antiviral (DAA) regimen active against all major types of hepatitis C virus (HCV) in untreated patients with compensated cirrhosis. High virological cure rates were achieved with glecaprevir/pibrentasvir across HCV genotypes 1–6, and these high cure rates did not depend on any patient or viral characteristics present before treatment. This may simplify care and allow non-specialist healthcare professionals to treat these patients, contributing to global efforts to eliminate HCV.

Introduction

Chronic HCV infection is a major public health threat, with an estimated 71 million individuals affected worldwide.[1] In 2015, it was estimated that only 20% of these individuals were aware of their HCV infection.[1] In 2016, approximately 13% of those aware of having chronic HCV infection were being treated.[2] Approximately 15–30% of patients with chronic HCV infection will develop cirrhosis within 20 years[3] and, if left untreated, these patients are at risk of developing hepatic decompensation and hepatocellular carcinoma, ultimately leading to increased liver-related mortality.[4] Successful treatment of chronic HCV infection can significantly reduce disease progression, as well as rates of HCV transmission.[5]

Keywords: Chronic HCV infection; Compensated cirrhosis; Direct-acting antiviral; Glecaprevir/pibrentasvir; HCV elimination; Hepatitis C virus; Pangenotypic; Short duration.

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The development of combination treatments comprising all-oral, interferon-free, direct-acting antiviral (DAA) drugs has substantially improved the efficacy and safety of HCV therapy. Recommended treatments are associated with high rates of sustained virological response at post-treatment week 12 (SVR12), low risk of HCV drug resistance, and treatment durations as short as 8 weeks for patients without cirrhosis.[6] However, patients with compensated cirrhosis are still considered more challenging to treat.[5,7] At the time of designing this study, DAA therapies recommended for the population with cirrhosis required at least 12 weeks of treatment, and no 8-week DAA regimen was approved for treatment-naïve patients with compensated cirrhosis (although 8 weeks of sofosbuvir/velpatasvir/voxilaprevir could be considered in DAA-naïve HCV genotype 3–infected patients with compensated cirrhosis in Europe).[8] Additional limitations for some approved regimens included the requirement for ribavirin, resistance testing, and monitoring for potential drug–drug interactions.[5,7] In a compensated cirrhotic population at risk of disease progression, an 8-week pangenotypic DAA regimen without such limitations may be preferable if SVR12 remains high. Furthermore, simplification of HCV care such that all treatment-naïve patients are treated for 8 weeks regardless of cirrhosis status may expand the number of healthcare professionals who can prescribe DAA therapy and increase the number of patients treated.[5]

Co-formulated glecaprevir (HCV NS3/4A protease inhibitor) and pibrentasvir (HCV NS5A inhibitor) is approved as a fixed-dose, once-daily, all-oral, ribavirin-free, pangenotypic combination therapy (glecaprevir/pibrentasvir) for the treatment of patients with chronic HCV genotype 1–6 infection without cirrhosis or with compensated cirrhosis.[9,10] Glecaprevir/pibrentasvir has shown potent pangenotypic activity against common amino acid substitutions of HCV that confer resistance to approved NS3/4A and NS5A inhibitors.[11–13] At the time of designing this study, in HCV treatment-naïve patients without cirrhosis, the approved treatment duration for glecaprevir/pibrentasvir was 8 weeks and was associated with an SVR12 rate of 97.5%.[9] In HCV treatment-naïve patients with compensated cirrhosis, the approved treatment duration was 12 weeks and was associated with an SVR12 rate of 98.0% overall[9] and 97.5% in HCV genotype 3–infected patients.[9,14]

The EXPEDITION-8 trial evaluated the efficacy and safety of glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotype 1–6 infection and compensated cirrhosis.

Patients and methods

Trial design and patients

EXPEDITION-8 was a single-arm, open-label, phase IIIb trial conducted at 94 sites in Bulgaria, Canada, the Czech Republic, France, Greece, Hungary, Ireland, Israel, Italy, Poland, Portugal, Romania, Russia, Spain, Taiwan, the United Kingdom, the United States and Puerto Rico, and Vietnam. The study was originally designed to enroll patients with HCV genotypes 1, 2, 4, 5, and 6, and was subsequently amended to include genotype 3–infected patients.

Enrolled patients were 18 years of age or older, with chronic HCV genotype 1–6 infection, and had a positive anti-HCV antibody test and a plasma HCV RNA viral load ≥1,000 IU/ml at screening. Patients were HCV treatment-naïve and had to have cirrhosis as documented by: i) liver biopsy with a METAVIR fibrosis score of 4 (or equivalent); ii) a FibroScan® (Echosens, Paris, France) score of ≥14.6 kPa; or iii) a FibroTest (BioPredictive SAS, Paris, France) score of ≥0.75 and an aspartate aminotransferase (AST)-to-platelet ratio index (APRI) of >2. For subject eligibility, liver biopsy results always superseded FibroScan or FibroTest/APRI results, and FibroScan results always superseded FibroTest/APRI results. Child-Pugh score was required to be 5 or 6 at screening. Patients with current or past evidence of Child-Pugh B or C classification or a history of liver decompensation were excluded from the analysis. Absence of hepatocellular carcinoma was confirmed at or within 3 months prior to screening by a negative ultrasound, computed tomography scan, or magnetic resonance imaging.

Patients were also excluded if they had evidence of HBV or HIV infection at screening, were coinfected with more than 1 HCV genotype, or had a functional transplanted solid organ and were using immunosuppression. Laboratory exclusion criteria were serum albumin <2.8 g/dl, total bilirubin >3.0 mg/dl, alanine aminotransferase (ALT) or AST >10× upper limit of normal (ULN), creatinine clearance rate (Cockcroft-Gault method) <50 ml/min, hemoglobin <10 g/dl, or platelet count <50,000 cells/mm^3.

The trial was conducted in accordance with the International Council for Harmonisation guidelines and ethical principles that have their origin in the Declaration of Helsinki. Institutional review board approval was obtained for each trial site. All patients had to give written informed consent. This trial is registered with ClinicalTrials.gov, number NCT03089944.

Procedures

All patients received oral glecaprevir/pibrentasvir 300 mg/120 mg once daily with food for 8 weeks. HCV genotype and subtype were determined using the Versant® HCV Genotype Inno-LiPA® Assay (version 2.0; Siemens Healthcare Diagnostics, Tarrytown, NY, USA). If the genotype was unable to be determined using this assay, the genotype and subtype were identified using Sanger sequencing of a region of the HCV NS5B gene by the central laboratory. HCV subtype was also determined by next-generation sequencing followed by neighbor-joining phylogenetic analysis of NS3/4A and/or NS5A consensus nucleotide sequences.

Plasma samples for determination of HCV RNA levels were collected at screening; at regular intervals during the treatment period; and at post-treatment weeks 4, 12, and 24 (or at discontinuation). HCV RNA levels were measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test (version 2.0; Roche Molecular Systems, Branchburg, NJ, USA), which has a lower limit of quantification (LLoQ) and lower limit of detection of 15 IU/ml.

Plasma samples for determination of glecaprevir and pibrentasvir concentrations were collected at weeks 1, 2, 4, and 8 during the treatment period or at the time of premature treatment discontinuation.

Baseline polymorphisms in NS3 at amino acid positions 155, 156, and 168, and in NS5A at amino acid positions 24, 28, 30, 31, 58, 92, and 93, were identified by next-generation sequencing using a 15% detection threshold for all patients with available samples, and sequences were analyzed relative to a subtype-specific reference sequence. For patients who experienced virological failure and had a post-baseline sample with HCV RNA ≥1,000 IU/ml, treatment-emergent resistance-associated substitutions (RASs) were assessed by next-generation sequencing

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using a 15% detection threshold in NS3 at amino acid positions 36, 43, 54, 55, 56, 80, 155, 156, 166, and 168, and in NS5A at amino acid positions 24, 28, 29, 30, 31, 32, 58, 92, and 93.

Safety of glecaprevir/pibrentasvir was assessed by monitoring adverse events from day 1 until 30 days after treatment completion (treatment-emergent period) and laboratory abnormalities. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 21.0) and the severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The severity of adverse events and their relationship to glecaprevir/pibrentasvir treatment were assessed by the investigator. The presence of hepatocellular carcinoma was assessed at screening and post-treatment week 24 (or at the time of premature study discontinuation), and at 6-month intervals between these visits. An ultrasound result suspicious of hepatocellular carcinoma was confirmed by computed tomography scan or magnetic resonance imaging.

Outcomes

The primary efficacy endpoints were the SVR12 rates in HCV genotype 1, 2, 4, 5, and 6–infected patients in the per protocol (PP) and intention-to-treat (ITT) populations. The key secondary efficacy endpoints were the SVR12 rates in HCV genotype 1–6-infected patients in the PP and ITT populations. Other secondary efficacy endpoints included the percentage of HCV genotype 3–infected patients in the PP and ITT populations who achieved SVR12, and the percentage of patients with on-treatment virological failure and post-treatment relapse across genotypes (in the ITT population).

SVR12 was defined as HCV RNA <LLoQ 12 weeks after the last dose of glecaprevir/pibrentasvir. On-treatment virological failure was defined as an increase in 2 consecutive HCV RNA measurements >1 $\log_{10}$ IU/ml above nadir during treatment, or 2 consecutive HCV RNA measurements ≥100 IU/ml after HCV RNA has fallen <LLoQ during treatment. Post-treatment relapse was defined as 2 consecutive HCV RNA measurements ≥LLoQ between the end of treatment and 12 weeks after the last dose of glecaprevir/pibrentasvir in patients who have completed treatment, with HCV RNA <LLoQ at the last treatment visit and at least 1 post-treatment HCV RNA measurement.

The ITT population was defined as all enrolled patients who received at least 1 dose of glecaprevir/pibrentasvir. The PP population was defined as the ITT population excluding patients who experienced virological breakthrough, discontinued treatment prior to week 8, or had missing SVR12 data.

Statistical analysis

The primary and key secondary efficacy analyses were to compare the lower bound of the 95% CI of the SVR12 rate in i) patients with genotypes 1, 2, 4, 5, and 6 in the PP population, ii) patients with genotypes 1, 2, 4, 5, and 6 in the ITT population, iii) patients with genotypes 1–6 in the PP population, and iv) patients with genotypes 1–6 in the ITT population, to efficacy thresholds that were pre-defined based on the historical SVR12 rates for 12 weeks of glecaprevir/pibrentasvir in the same patient populations.

The thresholds for the primary and key secondary efficacy analyses were based on the historical SVR12 rates of 100% in treatment-naïve patients with chronic HCV genotype 1–6 infection and compensated cirrhosis who were treated with 12 weeks of glecaprevir/pibrentasvir in the registrational program, which included 117 patients with genotypes 1, 2, 4, 5, and 6 and 65 patients with genotype 3, from the EXPEDITION-1,[15] SURVEYOR-II,[14,16] and EXPEDITION-4[17] studies. To establish the efficacy threshold for the PP population in EXPEDITION-8, a margin of 6% was applied to this historical SVR12, resulting in a threshold SVR12 rate of 94% for the PP population. Historical SVR12 rates are expected to be lower in an ITT population than in a PP population because the ITT population includes patients with non-virological failure (*e.g.*, patients who prematurely discontinue treatment or patients with missing SVR12 data). Thus, SVR12 rates in an ITT population may depend on the number of observed non-virological failures. The observed rate of non-virological failures in the registrational program was approximately 1%. Therefore, the historical SVR12 rate based on the ITT population was assumed to be 99% (PP SVR12 rate minus 1% non-virological failure rate). To establish the efficacy threshold for the ITT population in EXPEDITION-8, a margin of 6% was applied to the historical control rate of 99%, resulting in a threshold SVR12 rate of 93% for the ITT population.

The study was initially designed to enroll approximately 270 patients with genotypes 1, 2, 4, 5, and 6, and was then amended to include approximately 60 genotype 3–infected patients for a total of 330 patients with genotypes 1–6. With a sample size of 270 patients and assuming that 98% and 97% of the genotype 1, 2, 4, 5, and 6–infected patients in the PP and ITT populations, respectively, achieved SVR12, the study had over 80% power to demonstrate the efficacy of the 8-week treatment arm compared to the historical control SVR12 rate (defined by a 2-sided 95% lower confidence bound above 94% and 93% in the PP and ITT populations, respectively) for genotype 1, 2, 4, 5, and 6–infected patients. Similarly, with a sample size of 330 genotype 1–6-infected patients and assuming an SVR12 rate of 98% in the PP population and 97% in the ITT population, the study had over 80% power to demonstrate the efficacy of the 8-week treatment arm compared to the historical control SVR12 rate in the PP and ITT populations for genotype 1–6-infected patients.

The primary and key secondary efficacy analyses were tested through a fixed-sequence testing procedure as follows:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration is demonstrated if the lower bound of the 2-sided 95% CI for the percentage of HCV genotype 1, 2, 4, 5, and 6–infected patients in the PP population achieving SVR12 is >94%.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration is demonstrated if the lower bound of the 2-sided 95% CI for the percentage of HCV genotype 1, 2, 4, 5, and 6–infected patients in the ITT population achieving SVR12 is >93%.
3. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration is demonstrated if the lower bound of the 2-sided 95% CI for the percentage of HCV genotype 1–6-infected patients in the PP population achieving SVR12 is >94%.
4. Efficacy of the 8-week treatment duration compared with the historical 12-week treatment duration is demonstrated if the lower bound of the 2-sided 95% CI for the percentage of HCV genotype 1–6-infected patients achieving SVR12 in the ITT population is >93%.

The primary and key secondary efficacy analyses were tested using the hierarchical order outlined above to control the Type I

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error rate. Only if success was demonstrated for the first comparison would testing proceed to the second comparison, and so on. A backward imputation method was used to impute missing responses for SVR12. For all primary and key secondary efficacy analyses, the percentage of patients achieving SVR12 was summarized and a 2-sided 95% CI was calculated using the normal approximation to the binomial distribution, unless the number of patients who failed to achieve SVR12 was less than 5, then the Wilson's score method was used instead.

Safety was assessed in all patients who received at least 1 dose of glecaprevir/pibrentasvir. All analyses were conducted using Statistical Analysis System (SAS Institute, Inc., Cary, NC, USA).

For further details regarding the materials and methods used, please refer to the supplementary files provided.

Results

A total of 429 patients were screened between April 2017 and February 2019. Eighty-six patients were excluded, of whom 80 did not meet the eligibility criteria (Fig. 1). Overall, 343 treatment-naïve patients with chronic HCV genotype 1–6 infection and compensated cirrhosis received at least 1 dose of glecaprevir/pibrentasvir (ITT population). Of these, 342 patients completed treatment per the investigator. Eight patients were excluded from the PP population (n = 335): 1 patient discontinued treatment prior to week 8, 1 patient (who achieved SVR12) received treatment for <52 days, and 6 patients had missing SVR12 data.

Most patients were male (63%), white (83%), and had HCV genotype 1 infection (67%) (Table 1). At baseline, median HCV RNA level was 6.3 $\log_{10}$ IU/ml (Q1–Q3: 5.7–6.6), median albumin was 4.2 g/dl (Q1–Q3: 4.0–4.5), median total bilirubin was 12.0 µmol/L (Q1–Q3: 8.6–16.0), and median platelet count was 151 × 10^9/L (Q1–Q3: 110–188). Median FibroScan score was 20.2 kPa (Q1–Q3: 16.4–26.6) in 295 patients with available data; 4 patients who enrolled with FibroScan scores <14.6 kPa had liver biopsies demonstrating cirrhosis. Additional details on the methods used to diagnose cirrhosis for patient eligibility can be found in Table 2. Of the 285 patients enrolled based on FibroScan results, 173 had normal platelet counts at baseline, 66 had baseline ALT above 3× ULN, and 31 had both normal platelet counts and ALT above 3× ULN at baseline. A total of 90% of patients had a Child-Pugh score of 5 and 10% had a Child-Pugh score of 6. Three (<1%) patients had a Child-Pugh score of 7; of

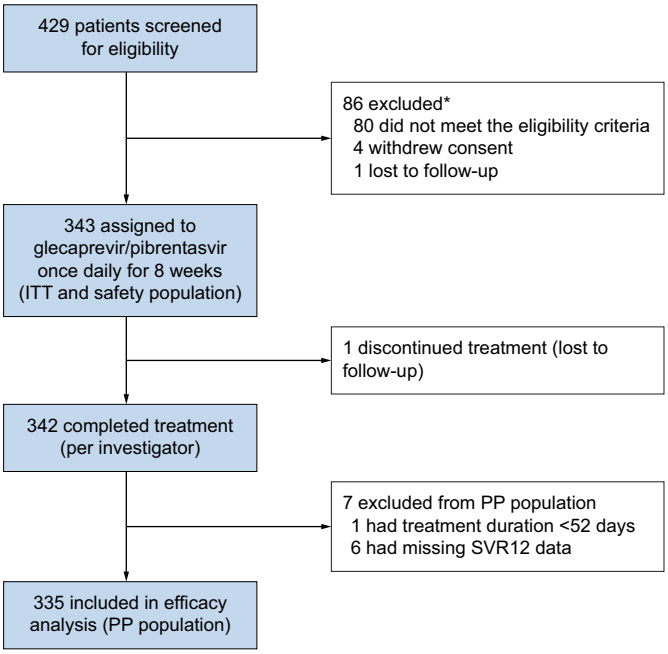

Fig. 1. Patient disposition. ITT, intention-to-treat; PP, per protocol; SVR12, sustained virological response at post-treatment week 12. *Patients who were screen failures were counted under each reason given for screen failure; therefore, the sum of the counts given for the reasons may be greater than the overall number of screen failures.

Table 1. Demographics and clinical characteristics at baseline.

	Patients (N = 343)
Male, n (%)	217 (63)
Age, median (Q1–Q3), years	58 (51–65)
Race, n (%)*	
White	285 (83)
Black	28 (8)
Hispanic or Latino ethnic origin, n (%)	43 (13)
Body mass index, median (Q1–Q3), kg/m^2	27.2 (24.5–31.1)
HCV genotype, n (%)†	
1	231 (67)
1a	95 (28)
1b	136 (40)
2	26 (8)
3	63 (18)
4	13 (4)
5	1 (<1)
6	9 (3)
IL28B non-CC genotype, n/N (%)	216/330 (65)
HCV RNA, median (Q1–Q3), $\log_{10}$ IU/ml	6.3 (5.7–6.6)
Patients diagnosed as cirrhotic based on:	
Histology showing Metavir F4 or equivalent, n (%)	32 (9)
FibroScan ≥14.6 kPa, n (%)	285 (83)
FibroTest ≥0.75 and APRI >2, n (%)	26 (8)
FibroScan score (n = 295), median (Q1–Q3)	20.2 (16.4–26.6)‡
Baseline Child-Pugh score, n (%)§	
5	307 (90)
6	33 (10)
>6	3 (<1)
Albumin, median (Q1–Q3), g/dl	4.2 (4.0–4.5)
Total bilirubin, median (Q1–Q3), µmol/L	12.0 (8.6–16.0)
Alanine aminotransferase, median (Q1–Q3), U/L	78.0 (49.0–116.0)
Platelet count × 10^9/L, median (Q1–Q3)	151 (110–188)
<100 × 10^9/L, n (%)	63 (18)
<150 × 10^9/L, n (%)	171 (50)
Injection drug use, n (%)‖	92 (27)
Patients on stable OST, n (%)	27 (8)
Baseline polymorphisms, n/N (%)¶	
None	218/335 (65)
NS3 only	4/335 (1)
NS5A only	111/335 (33)
NS3 and NS5A	2/335 (<1)

APRI, aspartate aminotransferase-to-platelet ratio index; OST, opioid substitution therapy. Q1 = 25th percentile. Q3 = 75th percentile.
*2 patients reported being multiracial.
†Final HCV genotype and subtype from phylogenetic analysis or the Versant HCV Genotype Inno-LiPA Assay Version 2.0 if phylogenetic result was not available.
‡Value includes all patients with a baseline FibroScan score.
§3 patients had a Child-Pugh score of 7 at baseline (2 had a score ≤6 at screening; 1 protocol deviation had a score of 7).
‖All but 4 patients reported injection drug use >12 months ago. Of note, unlike EXPEDITION-8, the case report form in the historical studies only captured patients with former injection drug use.
¶Baseline polymorphisms were assessed in NS3 at amino acid positions 155, 156, and 168, and in NS5A at amino acid positions 24, 28, 30, 31, 58, 92, and 93, for patients with available data in both targets.

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these, 2 patients had a Child-Pugh score of ≤6 at screening and 1 patient had a Child-Pugh score of 7 (a protocol violation). Of 335 patients with available baseline sequence data for both NS3 and NS5A, 4 patients (1%) had polymorphisms in NS3 only, 111 patients (33%) had polymorphisms in NS5A only, and 2 patients (<1%) had polymorphisms in both NS3 and NS5A (Table 1). Baseline demographics for the historical control cohort are shown in Table S1.

For patients with HCV genotypes 1, 2, 4, 5, and 6, the SVR12 rate was 100% (n/N = 274/274; 95% CI 98.6–100) in the PP population and 98.2% (n/N = 275/280; 95% CI 96.7–99.8) in the ITT population (Table 3). For patients with HCV genotypes 1–6, the SVR12 rate was 99.7% (n/N = 334/335; 95% CI 98.3–99.9) in the PP population and 97.7% (n/N = 335/343; 95% CI 96.1–99.3) in the ITT population. For all primary and key secondary efficacy analyses, the lower bound of the 95% CI for each SVR12 rate exceeded the corresponding pre-defined historical efficacy threshold (94% and 93% for the PP and ITT populations, respectively). Thus, the primary and key secondary efficacy objectives were met. No patient experienced on-treatment virological failure. One patient (genotype 3a–infected) experienced relapse at post-treatment week 4. One genotype 1b–infected patient prematurely discontinued treatment prior to week 8 for reasons other than adverse events. Six patients had missing SVR12 data (4 had genotype 1; 2 had genotype 3; all had undetectable HCV RNA levels at their last visit) (Table 3). SVR12 rates were similarly high across HCV genotypes (Fig. 2). For patients with HCV genotype 3, the SVR12 rate was 98.4% (n/N = 60/61; 95% CI 91.3–99.7) in the PP population and 95.2% (n/N = 60/63; 95% CI 86.9–98.4) in the ITT population. SVR12 rates were also high regardless of the presence or absence of baseline polymorphisms in NS3 or NS5A, including in patients with genotype 3. All patients with baseline polymorphisms who had documented SVR12 data achieved SVR12.

The genotype 3a–infected patient who relapsed had a relevant medical history of chronic pancreatitis, duodenal-gastric reflux, and cholecystectomy. Although this patient was adherent to study drug administration by pill count, their observed glecaprevir and pibrentasvir trough plasma concentrations were numerically lower throughout the treatment period compared with the median trough concentrations in all genotype 3–infected patients with compensated cirrhosis, as well as in patients infected with other genotypes, while still within the range of trough concentrations observed in these patients. The altered gastric motility and reduced pancreatic exocrine secretion may have impaired the absorption of glecaprevir/pibrentasvir in this patient. The patient did not have baseline polymorphisms in NS3 or NS5A; however, treatment-emergent A30K and Y93H in NS5A were detected at the time of failure; treatment-emergent RASs were not detected in NS3.

Overall, 158 (46%) patients experienced treatment-emergent adverse events (Table 4), the majority of which (100/158; 63%) had a maximum severity of grade 1. The most common adverse events (≥5%) were fatigue (9%), pruritus (8%), headache (8%), and nausea (6%). Six patients (2%) experienced serious adverse events, none of which were considered to be related to glecaprevir/pibrentasvir. One patient with low baseline leukocyte and neutrophil counts experienced isolated grade 3 leukopenia and neutropenia, with onset on post-treatment day 29, which were considered to be related by the investigator. No patient discontinued treatment because of an adverse event or died during the trial. One patient with a medical history of diabetic nephropathy and evidence of decompensated cirrhosis at screening (moderate ascites was present on screening ultrasound but was unrecognized at that time) enrolled as a protocol violation and experienced an event of worsening of ascites (grade 1) on day 8, which was ongoing at the end of the study. ALT and AST were normal at the onset of the adverse event and throughout the treatment period. This event was not considered to be related to glecaprevir/pibrentasvir and did not meet criteria for a serious adverse event; the patient completed treatment and achieved SVR12. No post-baseline cases of hepatocellular carcinoma were identified.

There were no grade 2 ALT or AST elevations. Grade 3 or higher laboratory abnormalities were infrequent (Table 4). One patient with a medical history of injection drug use and ongoing alcohol use experienced an isolated, asymptomatic grade 3 elevation in ALT on day 8, which subsequently resolved, without concomitant elevation in total bilirubin. Two patients experienced an isolated grade 3 decrease in neutrophil count. One patient with a baseline platelet count of 53×10^9/L experienced grade 3 decreases in platelet count during the post-treatment period. No patients experienced grade 3 or 4 elevations in AST or total bilirubin (Table 4). No patient discontinued treatment because of a laboratory abnormality. No liver-related toxicities or cases of drug-induced liver injury were observed.

Discussion

In EXPEDITION-8, treatment-naïve patients with chronic HCV genotype 1–6 infection and compensated cirrhosis received glecaprevir/pibrentasvir for 8 weeks and achieved SVR12 rates of 99.7% in the PP population and 97.7% in the ITT population. These rates exceeded the pre-defined historical SVR12 thresholds in these populations. The patients in this trial were representative of patients with compensated cirrhosis, as indicated by a median albumin level of 4.2 mg/dl, a median platelet count of 151×10^9/L, and 90% of patients having a Child-Pugh score of 5. The median FibroScan score of 20.2 kPa suggests that these compensated cirrhotic patients had significant, advanced fibrosis. Non-invasive methods for the diagnosis of cirrhosis have inherent limitations, for example FibroScan values can be falsely elevated because of liver inflammation. The current European Association for the Study of the Liver (EASL) guidelines recommend a FibroScan cut-off of 13 kPa for the diagnosis of cirrhosis.[7] In EXPEDITION-8, a more conservative cut-off of 14.6 kPa was used to minimize the occurrence of false-positive results. Of note, the population of treatment-naïve patients with compensated cirrhosis currently available for participation in clinical trials – including the glecaprevir/pibrentasvir registrational trials used as the historical control and EXPEDITION-8 itself – have less advanced disease, as most patients with more advanced cirrhosis were treated at the beginning of the DAA era. More importantly, the population of compensated cirrhotic patients enrolled in EXPEDITION-8 represents a population that is comparable to the patients with compensated cirrhosis in the historical cohort population (Table S1) and to the cirrhotic population enrolled in trials of earlier generation regimens.[18]

Treatment with glecaprevir/pibrentasvir for 8 weeks was well tolerated in HCV treatment-naïve patients with compensated cirrhosis. No patient discontinued treatment because of an adverse event and no serious adverse event was attributed to glecaprevir/pibrentasvir. Laboratory abnormalities of grade 3 or higher were infrequent. No cases of drug-induced liver

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Table 2. Method used to select cirrhotic patients for study.

Method used to determine cirrhosis eligibility	Patients diagnosed using each method, n	Platelet count (10^9/L) Patients with available data, n (median; Q1–Q3; min–max)	FibroScan score (kPa) Patients with available data, n (median; Q1–Q3; min–max)
Histology confirming Metavir F4 or equivalent	32	32 (173; 108.5–226; 62–326)	10 (15.2; 11.3–17.5; 2.5–35.8)
FibroScan ≥14.6 kPa (no histology data available)	285	285 (154; 112–190; 42–788)	285 (20.8; 16.6–26.7; 14.6–75)
FibroTest ≥0.75 and APRI >2 (no histology or FibroScan data available)	26	26 (103.5; 77–139; 51–211)	n.a.

APRI, aspartate aminotransferase-to-platelet ratio index; n.a., not applicable; Q1 = 25th percentile. Q3 = 75th percentile.

Table 3. Primary and key secondary efficacy endpoints for 8-week glecaprevir/pibrentasvir in treatment-naïve patients with chronic HCV genotype 1–6 infection and compensated cirrhosis.

	Primary efficacy endpoints, HCV genotypes 1, 2, 4, 5, and 6		Key secondary efficacy endpoints, HCV genotypes 1–6	
	PP population (N = 274)	ITT population (N = 280)	PP population (N = 335*)	ITT population (N = 343)
SVR12, n/N (%)	274/274 (100)	275/280 (98.2)	334/335 (99.7)	335/343 (97.7)
95% CI	98.6–100	96.7–99.8	98.3–99.9	96.1–99.3
Threshold, %	94	93	94	93
Non-response, n/N (%)	0/274	5/280 (1.8)	1/335 (0.3)	8/343 (2.3)
Reason for non-response, n/N (%)				
Virological failure	0/274	0/280	1/335 (0.3)	1/343 (0.3)
On-treatment virological failure	0/274	0/280	0/335	0/343
Relapse	0/271	0/274	1/332 (0.3)	1/336 (0.3)
Non-virological failure	0/274	5/280 (1.8)	0/335	7/343 (2.0)
Premature study drug discontinuation	0/274	1/280 (0.4)	0/335	1/343 (0.3)
HCV reinfection	0/274	0/280	0/335	0/343
Missing SVR12 data	0/274	4/280 (1.4)	0/335	6/343 (1.7)

ITT, intention-to-treat; PP, per protocol; SVR12, sustained virological response at 12 weeks post-treatment.
*8 patients (6 with genotype 1; 2 with genotype 3) were excluded from the PP population: 1 patient prematurely discontinued treatment prior to week 8, 1 patient (who achieved SVR12) received treatment for <52 days, and 6 patients had missing SVR12 data (all had undetectable HCV RNA levels at their last visit).

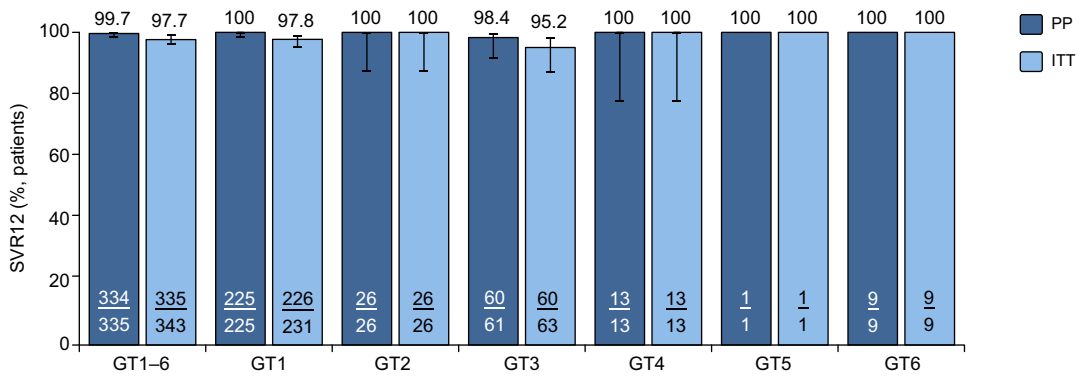

Fig. 2. SVR12 rates with 8-week glecaprevir/pibrentasvir in the PP and ITT populations, by HCV genotype. Error bars represent 95% CIs. GT, genotype; ITT, intention-to-treat; PP, per protocol; SVR12, sustained virological response at post-treatment week 12.

injury or hepatocellular carcinoma were reported. One patient with a medical history of diabetic nephropathy and evidence of decompensated cirrhosis at screening (moderate ascites was present on screening ultrasound but was unrecognized at that time) enrolled as a protocol violation and experienced a non-related, grade 1 adverse event of ascites at day 8, which was ongoing at the end of the study; this patient completed treatment and achieved SVR12. Overall, no new safety signals were observed during this trial and the safety profile was consistent with the approved label.[9,10]

International HCV treatment guidelines currently recommend DAA therapy for at least 12 weeks in treatment-naïve patients with chronic HCV genotype 1–6 infection and compensated cirrhosis.[3,5,7] In addition to glecaprevir/pibrentasvir, current treatment options for this patient population range from 8 to 24 weeks in duration and include elbasvir/grazoprevir (genotypes 1 and 4), ledipasvir/sofosbuvir (genotypes 1 and 4), and sofosbuvir/velpatasvir (genotypes 1–6).[5,7] However, not all of these options are equally potent across all major HCV genotypes and some patient subgroups may require viral resistance testing or ribavirin as part of their recommended treatment regimen.[5,7] Alternative DAA options are available for this population – sofosbuvir/velpatasvir/voxilaprevir and ombitasvir/paritaprevir/ritonavir plus dasabuvir – although current guidelines only recommend these regimens for certain genotypes in treatment-naïve patients with compensated cirrhosis.[5,7] The only DAA options available for treatment-naïve patients with cirrhosis with genotype 3 are the pangenotypic regimens

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glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir. However, sofosbuvir/velpatasvir is not recommended by EASL in patients with cirrhosis with genotype 3 in the presence of baseline NS5A polymorphisms or in the absence of baseline resistance testing (otherwise, it requires the addition of ribavirin),[7,19] and sofosbuvir/velpatasvir/voxilaprevir is not licensed for treatment-naïve patients in the United States.[20] At the time of the design of the EXPEDITION-8 study, there were no pangenotypic regimens approved for 8 weeks in all treatment-naïve patients with compensated cirrhosis. Based on the results of this study, the European Medicines Agency has granted marketing authorization for glecaprevir/pibrentasvir to be used for 8 weeks in treatment-naïve patients with HCV genotypes 1, 2, 4, 5, or 6 and compensated cirrhosis (at the time of the writing of this manuscript, data for genotype 3–infected patients are in the process of being submitted to the European Medicines Agency for evaluation)[21] and the US Food and Drug Administration has approved the use of glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1–6 and compensated cirrhosis.[22]

Studies investigating 8-week treatment durations with the recommended DAA regimens in treatment-naïve patients with compensated cirrhosis have been limited to date. In the POLARIS-2 trial,[23] 8 weeks of sofosbuvir/velpatasvir/voxilaprevir treatment resulted in an SVR12 rate of 91% (n/N = 82/90) in DAA-naïve patients with compensated cirrhosis who were infected with HCV genotypes 1, 2, 4, 5, or 6, and the regimen failed to demonstrate non-inferiority to 12 weeks of sofosbuvir/velpatasvir in the overall population; the lower efficacy in the sofosbuvir/velpatasvir/voxilaprevir arm was driven by the lower rates of SVR12 in genotype 1a– and 4–infected patients (92%). In the POLARIS-3 trial,[23] 8 weeks of sofosbuvir/velpatasvir/voxilaprevir resulted in an SVR12 rate of 96% (n/N = 106/110) in DAA-naïve genotype 3–infected patients with compensated cirrhosis, which was superior to the performance goal of 83%. In the C-SWIFT trial,[24] 8 weeks of elbasvir/grazoprevir plus sofosbuvir treatment resulted in an SVR12 rate of 81% (n/N = 17/21) in treatment-naïve genotype 1–infected patients with compensated cirrhosis. In the ACCORDION study,[25] 8 weeks of simeprevir, daclatasvir, and sofosbuvir in a small number of treatment-naïve genotype 1–infected patients with compensated cirrhosis resulted in an SVR12 rate of 100% (n/N = 9/9). The study reported here, EXPEDITION-8, is the first phase III trial to demonstrate the efficacy of an 8-week DAA regimen across HCV genotypes 1–6 in treatment-naïve patients with compensated cirrhosis.

Table 4. Treatment-emergent adverse events and post-baseline laboratory abnormalities.

	Patients (N = 343)
Adverse events, n (%)	
Any AE	158 (46)
Any AE of grade ≥3	11 (3)
Any serious AE*	6 (2)
Any drug-related serious AE	0
Any drug-related AE of grade ≥3†	1 (<1)
Any AE leading to discontinuation of study drug	0
AEs occurring in ≥5% of patients	
Fatigue	30 (9)
Pruritus	29 (8)
Headache	28 (8)
Nausea	19 (6)
Deaths‡	0
Laboratory abnormalities (grade ≥3), n/N (%)§	
Alanine aminotransferase (>5× ULN)	1/342 (<1)
Aspartate aminotransferase (>5× ULN)	0/342
Total bilirubin (>3× ULN)	0/342
Hemoglobin (<8 g/dl)	0/342
Neutrophil count (<1.0 × 10^9/L)	2/342 (<1)
Platelet count (<50.0 × 10^9/L)	1/341 (<1)

AE, adverse event; ULN, upper limit of normal.
*Duodenal ulcer hemorrhage and gastric adenocarcinoma (n = 1); pyelonephritis (n = 1); atrial fibrillation and cardiac failure (n = 1); peripheral edema (n = 1); pneumonia (n = 1); bronchitis (n = 1).
†Leukopenia and neutropenia (n = 1).
‡Includes non–treatment-emergent deaths.
§No grade 4 laboratory abnormalities were reported.

Improving access to DAA therapies has become a global priority to help meet the World Health Organization's goal of eliminating HCV as a major public health threat by 2030.[1] Despite the availability of highly efficacious and well-tolerated pangenotypic DAA drugs, such as glecaprevir/pibrentasvir, HCV management strategies recommended by current guidelines[5,7] remain relatively complex and may present a barrier to treatment access. For example, numerous pre-treatment assessments, including cirrhosis assessment, are recommended prior to treatment initiation. A universal treatment duration of 8 weeks for all treatment-naïve patients, regardless of cirrhosis status, could minimize the burden of pre-treatment assessments as well as help reduce healthcare costs. This benefit is especially relevant as the epidemiology of HCV infection is shifting towards a predominantly treatment-naïve population.[29]

One limitation of this trial is the relatively low number of patients with HCV genotype 5 or 6 infection, despite no restrictions imposed on their enrollment. This reflects the relatively low prevalence of these genotypes in the regions where the trial was conducted. All patients with genotype 5 or 6 infection achieved SVR12. Furthermore, half-maximal effective concentration (EC50) values for glecaprevir and pibrentasvir in genotype 5 or 6 are similar to those in genotype 1 in the *in vitro* HCV stable replicon assay;[11,13] patients with genotype 1 infection were well represented in this trial and achieved an SVR12 rate of 97.8%. More importantly, the SVR rate among genotype 3–infected patients, considered more difficult to treat than those with genotype 5 or 6, was 95.2% with only 1 virological failure, supporting the pangenotypic efficacy of glecaprevir/pibrentasvir for 8 weeks in all treatment-naïve patients with compensated cirrhosis.

In treatment-naïve patients with chronic HCV genotype 1–6 infection and compensated cirrhosis (as identified per current standard diagnostic methods), the once daily, oral, fixed-dose combination of glecaprevir/pibrentasvir for 8 weeks was well

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tolerated and led to very high SVR12 rates, comparable to those demonstrated with a 12-week treatment duration. Based on the results of this study, glecaprevir/pibrentasvir for 8 weeks is now approved for the treatment of treatment-naïve patients with compensated cirrhosis. Shortening treatment duration in this population may support efforts to simplify the HCV care pathway, furthering the progress towards HCV elimination.

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, AST-to-platelet ratio index; DAA, direct-acting antiviral; ITT, intention-to-treat; LLoQ, lower limit of quantification; OST, OST, opioid substitution therapy; PP, per protocol; ULN, upper limit of normal.

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Conflicts of interest

RS Brown Jr: Research support from AbbVie, Gilead, Merck, Intercept, and Bristol-Myers Squibb, and has acted as an advisor for AbbVie, Bristol-Myers Squibb, Gilead, Intercept, Merck, Shionogi, and Dova. M Buti: Advisory board/speaker for Gilead, AbbVie, Merck, and Janssen. V Chulanov: Advisory board/speaker for Gilead, AbbVie, Merck, Bristol-Myers Squibb, Janssen, and R-Pharm; investigator in clinical trials sponsored by AbbVie, Gilead, Bristol-Myers Squibb, and R-Pharm. WL Chuang: Investigator in AbbVie-sponsored clinical trials, and advisory board for Gilead, AbbVie, Bristol-Myers Squibb, MSD, and PharmaEssentia; and a speaker for Gilead, AbbVie, Bristol-Myers Squibb, MSD, and PharmaEssentia. H Aguilar: Grants from AbbVie. G Horváth: Consultant and/or an investigator for, and has received consulting/speaker fees from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Fresenius-Kabi, Gilead Sciences, Janssen, Cilag, MSD/Merck, and Roche. E Zuckerman: Advisory board/speaker for AbbVie, Gilead, Merck, and Intercept. B Rosado Carrion: Investigator in an AbbVie-sponsored clinical trial; speaker for AbbVie and Gilead. F Rodriguez-Perez: Investigator in an AbbVie-sponsored clinical trial; advisory board/speaker for AbbVie, Gilead, Intercept, and Merck. P Urbánek: Consultant for Gilead and MSD; research funding from Gilead; and speaker fees from AbbVie, MSD, and Gilead. A Abergel: Advisory board/speaker for AbbVie, Gilead, and Merck. C-W Lin: Former employee of AbbVie and may hold stock or options. F Felizarta: Research support from AbbVie, Janssen, and Merck; and speaker for AbbVie, Gilead, and Merck. L Rodrigues, E Cohen, SS Lovell, G Schnell, J Zha, S Wang, R Trinh, FJ Mensa, and M Burroughs: Employees of AbbVie, Inc., and may hold stock or options

Authors' contributions

RSB, LR, EC, SSL, GS, C-WL, SW, RT, and FJM conceived or designed the trial. SSL led statistical analyses, JZ led pharmacokinetic analyses, and GS led resistance analyses. RSB, MB, VC, W-LC, AA, HA, GH, EZ, BRC, FR-P, FF, and PU recruited and treated patients in the trial. All authors reviewed and approved the final version of the article.

Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (*e.g.*, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.10.020.

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