Efficacy and Safety of Glecaprevir/Pibrentasvir Treatment for 8 Weeks in Treatment-Naïve Patients With Chronic Hepatitis C Virus Infection Without Cirrhosis or With Compensated Cirrhosis: Analysis of Data Pooled From Phase 2 and 3 Studies

THU-198

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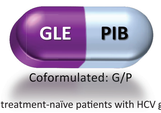
BACKGROUND

- Glecaprevir/pibrentasvir (G/P), a once-daily, all-oral, fixed-dose direct-acting antiviral (DAA) combination, is approved for adults chronically infected with hepatitis C virus (HCV) genotypes (GT) 1–6[1]
- In HCV treatment-naïve patients, G/P is currently approved for 8 weeks in patients without cirrhosis and 12 weeks in patients with compensated cirrhosis[1]
- A recent post-approval study of G/P administered for 8 weeks in HCV treatment-naïve cirrhotic patients with HCV GT1, 2, or 4–6 showed a high rate of sustained virologic response at post-treatment Week 12 (SVR12)[2]

G/P is Approved for Patients With HCV GT1–6 Infection

Glecaprevir
pangenotypic NS3/4A protease inhibitor



Coformulated: G/P

Pibrentasvir
pangenotypic NS5A inhibitor

- 8-week duration approved for treatment-naïve patients with HCV genotype (GT) 1–6 infection and without cirrhosis[1]
- Pangenotypic SVR12 rate of 98% in more than 2200 patients in registrational studies
- Potent against common polymorphisms (eg, Y93H in NS5A and Q80K in NS3)
- Favorable safety profile irrespective of baseline factors
- Recent real-world results demonstrate that G/P achieved high SVR12 rates consistent with those observed in clinical trials[3,4]

G/P dosed as 3 pills taken once daily with food for a total dose of 300 mg/120 mg. Glecaprevir was identified by AbbVie and Enanta.

OBJECTIVE

- To evaluate the efficacy and safety of G/P treatment for 8 weeks in HCV treatment-naïve patients with chronic HCV GT1, 2, or 4–6 infection without cirrhosis or with compensated cirrhosis in a pooled analysis of pre-approval and post-approval studies

METHODS

- Data were pooled from 8 Phase 2b, 3a, and 3b clinical trials of G/P: SURVEYOR-1[5] (Part 2; ClinicalTrials.gov identifier: NCT02243280), SURVEYOR-2[5,6] (Part 2 and Part 4; NCT02243293), ENDURANCE-1[7] (NCT02604017), EXPEDITION-2[8] (NCT02738138), ENDURANCE-5,6[9] (NCT02966795), EXPEDITION-5[10] (NCT03069365), EXPEDITION-8[2] (NCT03089944), and the aspartate aminotransferase-to-platelet ratio index (APRI) study[11] (NCT03212521)
- Patients received 8 weeks of oral, once daily G/P 300/120 mg

KEY ELIGIBILITY CRITERIA

- Patients aged ≥18 years
- Chronic HCV GT1, 2, or 4–6 infection
- Without cirrhosis or with compensated cirrhosis
  - Cirrhosis assessment was based on liver biopsy, FibroScan® (Echosens, Waltham, MA, USA), or a combination of FibroTest™ (BioPredictive, Paris, France) and APRI
  - Cirrhosis was defined as FibroScan ≥12.5 kPa (EXPEDITION-8, SURVEYOR-1 and 2 ≥14.6 kPa), FibroTest ≥0.75, or APRI >2
  - For the APRI study, cirrhosis assessment was based only on APRI[11]
- HCV treatment-naïve

ENDPOINTS AND ASSESSMENTS

- Percentage of patients with SVR12, defined as an HCV RNA level below the lower limit of quantification at post-treatment Week 12
- SVR12 rates for subgroups of interest
- Treatment-emergent adverse events (AEs) and post-baseline clinical laboratory abnormalities

ANALYSIS POPULATIONS

- The analysis population included all patients who received ≥1 dose of G/P (intention-to-treat [ITT] analysis)
- A modified ITT (mITT) analysis was also conducted for SVR12 that excluded patients with non-virologic failure (patients who discontinued treatment or were lost to follow-up)

RESULTS

- Of 1163 patients, 280 had cirrhosis. Most patients were white and had HCV GT1 or GT2; median age was 54 years
- Demographics and clinical characteristics at baseline are summarized in **Table 1**

Table 1. Demographics and Clinical Characteristics at Baseline

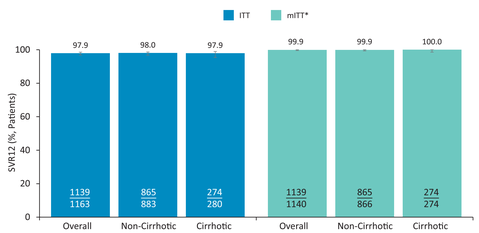
	Non-cirrhotic (N = 883)	Cirrhotic (N = 280)	Overall (N = 1163)
Male	460 (52)	168 (60)	628 (54)
Age, median, years	53	60	54
<65 years	764 (87)	196 (70)	960 (83)
Race			
White	697 (79)	223 (80)	920 (79)
Black	73 (8)	27 (10)	100 (9)
Asian	103 (12)	28 (10)	131 (11)
Other	10 (1)	2 (<1)	12 (1)
Ethnicity			
Hispanic or Latino	97 (11)	35 (13)	132 (11)
BMI, mean, kg/m^2	26.4	28.2	26.8
≥30 kg/m^2	174/882 (20)	81 (29)	255/1162 (22)
HCV GT			
1	504 (57)	231 (83)	735 (63)
2	234 (27)	26 (9)	260 (22)
4	62 (7)	13 (5)	75 (6)
5/6	19 (2)/64 (7)	1 (<1)/9 (3)	20 (2)/73 (6)
Fibrosis stage			
F0–F1	577/880 (66)	0	577/1160 (50)
F2	42/880 (5)	0	42/1160 (4)
F3	66/880 (8)	0	66/1160 (6)
F4	0	280 (100)	280/1160 (24)
HCV RNA, IU/mL			
≥1 000 000	550 (62)	190 (68)	740 (64)
Polymorphism*			
NS3 only	17/825 (2)	3/272 (1)	20/1097 (2)
NS5 only	137/825 (17)	46/272 (17)	183/1097 (17)
NS3 and NS5A	3/825 (<1)	0	3/1097 (<1)
None	668/825 (81)	223/272 (82)	891/1097 (81)
Platelet count			
<100 × 10^9/L	6 (<1)	48 (17)	54 (5)
APRI			
≥1	118/869 (14)	171/270 (63)	289/1139 (25)
≥2	21/869 (2)	92/270 (34)	113/1139 (10)
FibroTest™			
≥0.72	38/533 (7)	191/278 (69)	229/811 (28)
FIB-4			
≥3.25	38/869 (4)	141/270 (52)	179/1139 (16)
History of injection drug use	323/882 (37)	72 (26)	395/1162 (34)
Stable OST	49 (6)	17 (6)	66 (6)
HIV coinfection	109 (12)	0	109 (9)
History of diabetes	58 (7)	56 (20)	114 (10)
History of depression or bipolar disorder	186 (21)	8 (3)	194 (17)
History of CV disease	276 (31)	124 (44)	400 (34)

Data are n (%) or n/N (%) unless otherwise stated; percentages are calculated from non-missing values.
*For patients with available data in both target sequences, baseline polymorphisms were assessed relative to subtype-specific reference sequence at a 15% detection threshold in NS3 at amino acid positions 155, 156, and 168, and in NS5A at amino acid positions 28, 30, 31, 93, HS80, and 662A for GT1a; 31 and 93 for GT1b; 24, 28, 30, 92, and 93 for GT2; 24, 28, 30, 31, and 93 for GT4; and 24, 28, 30, 31, 58, 92, and 93 for GT5 and GT6.
APRI, aspartate aminotransferase-to-platelet ratio index; BMI, body mass index; CV, cardiovascular; FIB-4, fibrosis-4; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OST, opioid substitution therapy; RNA, ribonucleic acid.

EFFICACY

- Overall ITT and mITT SVR12 rates were 97.9% (95% confidence interval [CI] 96.9–98.6) and 99.9% (95% CI 99.5–100), respectively **(Figure 1)**
- A single patient without cirrhosis experienced virologic failure (relapse); no virologic failures were observed in patients with compensated cirrhosis **(Table 2)**
- SVR12 rates were high (>95%) regardless of cirrhosis status **(Figure 1)** or clinical markers of advanced liver disease **(Figure 2)**

Figure 1. SVR12 Rates After G/P Treatment for 8 Weeks by Cirrhosis Status



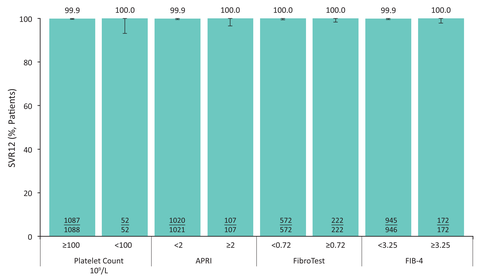
Error bars represent 95% confidence intervals.
*mITT population excluded patients with non-virologic failure.
G/P, glecaprevir/pibrentasvir; ITT, intention-to-treat; mITT, modified ITT; SVR12, sustained virologic response at post-treatment Week 12.

Table 2. Reasons for Non-Response (ITT)

Reasons for non-response, n (%)	Non-cirrhotic (N = 883)	Cirrhotic (N = 280)	Overall (N = 1163)
On-treatment virologic failure	0	0	0
Relapse	1/871 (<1)	0	1/1145 (<0.1)
Non-virologic failure			
Study drug discontinuation	9 (1)	1 (<1)	10 (<1)
Lost to follow-up*	8 (<1)	5 (2)	13 (1)

*Some patients are missing data as studies are ongoing.
ITT, intention-to-treat.

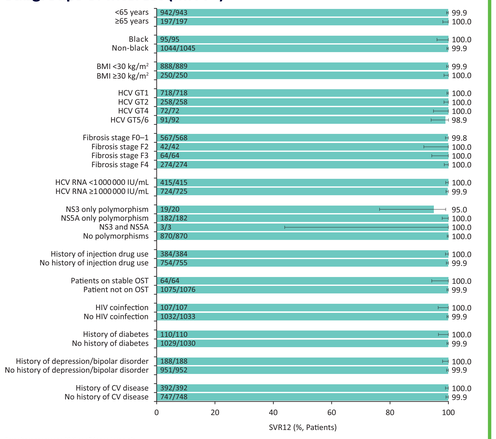
Figure 2. SVR12 Rates After G/P Treatment for 8 Weeks by Clinical Markers of Advanced Liver Disease (mITT*)



Error bars represent 95% confidence intervals.
*mITT population excluded patients with non-virologic failure.
APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; G/P, glecaprevir/pibrentasvir; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment Week 12.

- SVR12 rates in the mITT population were not affected by any baseline characteristic **(Figure 3)**

Figure 3. SVR12 Rates After G/P Treatment for 8 Weeks by Subgroups of Interest (mITT*)



Error bars represent 95% confidence intervals.
*mITT population excluded patients with non-virologic failure. BMI, body mass index; CV, cardiovascular; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; mITT, modified intention-to-treat; OST, opioid substitution therapy; RNA, ribonucleic acid; SVR12, sustained virologic response at post-treatment Week 12.

SAFETY

- The most common AEs (≥10%) were headache (11%) and fatigue (10%) **(Table 3)**
- Both DAA-related serious AEs and AEs leading to premature G/P discontinuation occurred in less than 1% of patients; all of these events occurred in non-cirrhotic patients
- Less than 1% of patients (n = 4) experienced hepatic laboratory abnormalities of Grade ≥3 in severity (ie, isolated aspartate aminotransferase elevation [n = 1] or isolated total bilirubin elevation [n = 3]). None of the cases were consistent with drug-induced liver injury

Table 3. Treatment-Emergent AEs and Post-Baseline Clinical Laboratory Abnormalities

AEs, n (%)	Overall (N = 1163)
Any AE	662 (57)
Any serious AE	30 (3)
Any AE possibly related to DAA	357 (31)
Any serious AE possibly related to DAA	2 (<1)
Any AE leading to discontinuation	4 (<1)
Deaths	1 (<0.1)
AEs in ≥10% of all patients	
Headache	126 (11)
Fatigue	122 (10)
Laboratory abnormalities, n/N (%)	**Overall (N = 1163)**
Alanine aminotransferase	
Grade ≥3	0/1157
Aspartate aminotransferase	
Grade ≥3	1/1157 (<0.1)
Total bilirubin	
Grade ≥3	3/1157 (<1)

AE, adverse event; DAA, direct-acting antiviral.

CONCLUSIONS

- G/P for 8 weeks was highly efficacious in HCV treatment-naïve patients with chronic HCV GT1, 2, or 4–6 infection, regardless of cirrhosis status
- Eight weeks of G/P yielded high SVR12 rates in patients with clinical markers of advanced liver disease and regardless of any other baseline characteristics
- G/P was well tolerated; treatment-related serious AEs and discontinuations due to AEs and laboratory abnormalities of Grade ≥3 were rare and were not consistent with drug-induced liver injury

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