Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients With HCV Genotype 5 or 6 Infection: An Integrated Analysis of Phase 2 and 3 Studies

THU-194

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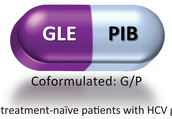
INTRODUCTION

- Chronic hepatitis C virus (HCV) infection affects approximately 71 million individuals worldwide.[1] However, HCV genotype (GT) 5 and GT6 infections account for less than 5% of infections worldwide[2,3]
- HCV is characterized by high genetic diversity, and the prevalence of each GT varies by geographical location.[3] GT5 has only 1 known subtype (GT5a), whereas GT6 exhibits high subtype diversity with 24 confirmed subtypes (GT6a-xa).[4] The efficacy data for GT6 subtypes are limited
- To help further the WHO goal of achieving HCV elimination by 2030, a potent pangenotypic short duration regimen that is active across the diverse array of HCV subgenotypes is necessary

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

Glecaprevir
pangenotypic NS3/4A protease inhibitor



Pibrentasvir
pangenotypic NS5A inhibitor

- 8-week duration approved for treatment-naïve patients with HCV genotype (GT) 1–6 infection and without cirrhosis[5]
- 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[6,7]

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.

- Efficacy and safety of glecaprevir 300 mg + pibrentasvir 120 mg (GLE + PIB) or coformulated glecaprevir 300 mg and pibrentasvir 120 mg (G/P) in HCV GT5- or HCV GT6-infected patients have been studied across 10 AbbVie Phase 2b, 3a (registrational) and 3b (post-registrational) studies[8,9]; the data analysis presented here integrates these data

OBJECTIVE

- To evaluate efficacy and safety of GLE + PIB co-administration or G/P coformulation in a pooled analysis of Phase 2b, 3a, and 3b data in HCV GT5- or HCV GT6-infected patients without cirrhosis or with compensated cirrhosis

DISCLOSURES

The design, study conduct, analysis, and financial support of this integrated analyses were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the content. All authors had access to all relevant data and participated in writing, review, and approval of the final presentation.

T Asselah: Clinical Investigator/Speaker/Consultant: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

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BB Yao, L Fredrick, G Schnell, F Mensa: Employees of AbbVie and may hold AbbVie stock or options.

METHODS

- Pooled data from 10 Phase 2b, 3a, and 3b studies were analyzed (**Table 1**). Patients with chronic HCV GT5 or GT6 infection received oral GLE + PIB or G/P once daily for either 8 or 12 weeks depending on the design of the original study

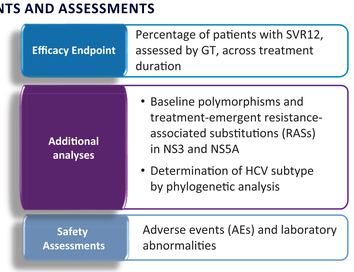
Table 1. HCV GT5- and GT6-Infected Patients Enrolled Per Study

Source study name	Patients, n (%) N = 181
ENDURANCE-56	84 (47)
ENDURANCE-4 (NCT02636595)	45 (25)
SURVEYOR-1	12 (7)
SURVEYOR-2	12 (7)
EXPEDITION-8	10 (6)
EXPEDITION-1	9 (5)
EXPEDITION-2	3 (2)
MAGELLAN-2	2 (1)
EXPEDITION-4	2 (1)
M16-133	2 (1)

KEY ELIGIBILITY CRITERIA

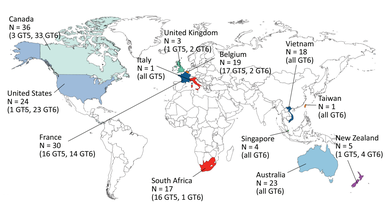
- ≥18 years of age
- BMI ≥18 kg/m^2
- Chronic HCV GT5 or GT6 infection (HCV RNA ≥1000 IU/mL)
- HCV treatment-naïve or treatment-experienced with regimens containing interferon (IFN) or pegylated IFN (pegIFN) ± ribavirin (RBV) or sofosbuvir (SOF) + RBV ± pegIFN
- Without cirrhosis or with compensated cirrhosis (Child-Pugh score of ≤6 and no history of Child-Pugh B or C)

ENDPOINTS AND ASSESSMENTS



RESULTS

Figure 1. Geographical Distribution of Enrolled HCV GT5- and GT6-Infected Patients



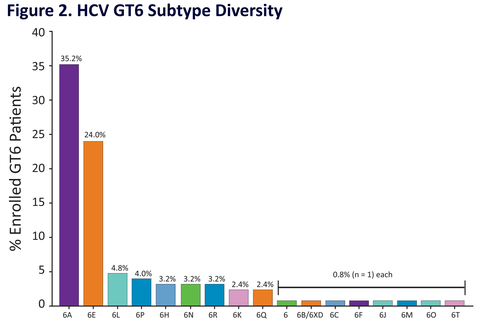
RESULTS (CONTINUED)

Table 2. Baseline Demographics and Disease Characteristics of HCV GT5- and GT6-Infected Patients

Characteristic	GT5 N = 56*	GT6 N = 125	Total N = 181
Male, n (%)	29 (52)	69 (55)	98 (54)
Age, median (range), years	64.5 (20–76)	54 (28–79)	56 (20–79)
BMI, median (range), Kg/m^2	28 (19.8–43.5)	23.4 (17.2–40)	24.3 (17.2–43.5)
Race, n (%)			
Asian	3 (6)	112 (90)	115 (65)
White	43 (81)	11 (9)	54 (30)
Black or African American	5 (9)	0	5 (3)
American Indian or Alaska Native	0	1 (1)	1 (1)
Multi-race	2 (4)	1 (1)	3 (2)
Missing[†]	3	0	3
HCV RNA ≥1 000 000 IU/ml, n (%)	39 (70)	102 (82)	141 (78)
HCV-treatment-experienced, n (%)[‡]	10 (18)	12 (10)	22 (12)
Fibrosis stage, n (%)			
F0–F1	40 (71)	83 (67)	123 (69)
F2	8 (14)	2 (2)	10 (6)
F3	2 (4)	16 (13)	18 (10)
F4	6 (11)	22 (18)	28 (16)
Missing[†]	0	2	2
Baseline Polymorphisms, n (%)[§]			
NS3 only	23 (42)	0	23 (15)
NS5A only	3 (5)	57 (56)	60 (38)
NS3 and NS5A	4 (7)	3 (3)	7 (4)
None	25 (45)	41 (41)	66 (42)
Missing[†]	1	24	25
History of injection drug use, n (%)	1 (2)	17 (4)	18 (10)
Treatment duration, n (%)			
8 weeks	23 (41)	79 (63)	102 (56)
12 weeks	33 (59)	46 (37)	79 (44)

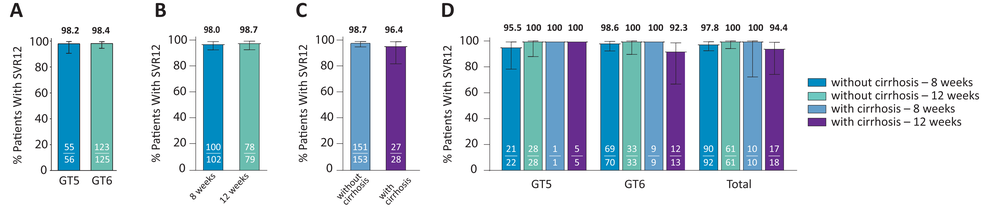
BMI, body mass index.
*All patients were subtype 5a.
[†]Missing not included in calculation of percentage.
[‡]No patients with SOF-experience enrolled.
[§]Baseline polymorphisms assessed relative to subtype-specific reference sequence at a 15% detection threshold in NS3 at amino acid positions 155, 156, and 168, and in NS5A at amino acid positions 24, 28, 30, 31, 58, 92, and 93 for patients with available data in both target sequences.
Note: Sums of percentages may differ from 100% due to rounding.

Figure 2. HCV GT6 Subtype Diversity



- One HCV GT5 subtype (5a) and 16 HCV GT6 subtypes were identified by phylogenetic analysis among 181 GT5/6-infected patients. Among HCV GT6-infected patients, the predominant subtypes were 6a (35%) and 6e (24%). One HCV GT6-infected patient was not assigned a subtype due to lack of homology to any of the known HCV GT6 subtypes
- Fifteen patients were missing subtype information by phylogenetic analysis due to technical reasons. Of these, 1 was HCV GT5a and 14 were HCV GT6 as determined by the Inno-LiPA 2.0 assay

Figure 3. SVR12 in HCV GT5- and GT6-Infected Patients by A. Genotype, B. Treatment Duration, C. Cirrhosis Status, D. Genotype, Treatment Duration, and Cirrhosis Status



- The overall SVR12 rate was 98.3% (178/181, 95% CI: 95.2% to 99.4%)

Table 3. Characteristics of HCV GT5- and GT6-Infected Patients With Virologic Failure

Characteristic	Patient 1 (OTVF at TW12)	Patient 2 (Relapse at PTW12)	Patient 3* (Relapse at PTW24)
Sex	Male	Male	Male
Age, years	71	54	30
Race	White	White	Asian
Genotype/subtype	6f	5a	6k
Cirrhosis status	Compensated cirrhosis	No cirrhosis	No cirrhosis
Prior treatment experience	None	None	None
Baseline HCV RNA, IU/mL	625 000	10 800 000	244 000
DAA adherent[†]	Yes	Yes	Yes
NS3 baseline polymorphisms[‡]	None	D168E	Data not available
NS5A baseline polymorphisms[‡]	None	None	None
NS3 RAS at the time of failure[‡]	A156M	None[§]	Data not available
NS3 RAS at the time of failure[‡]	T93A	None	None

DAA, direct-acting antiviral; PTW, post-treatment week; OTVF, on-treatment virologic failure; TW, treatment week; RAS, treatment-emergent resistance-associated substitution.
*Patient achieved SVR12 but relapsed at PT Week 24.
[†]Adherence measured by pill count.
[‡]Baseline polymorphisms and treatment-emergent resistance-associated substitutions were assessed in NS3 at amino acid positions 36, 43, 54, 55, 56, 80, 155, 156, and 168, and in NS5A at amino acid positions 24, 28, 29, 30, 31, 32, 58, 92, and 93.
[§]NS3 D168E was present at baseline and at the time of failure.

Table 4. Safety and Tolerability of HCV GT5- and GT6-Infected Patients

Event, n (%)	Total N = 181
Any adverse event (AE)	105 (58)
Any AE with a reasonable possibility of being related to G/P	63 (35)
Any AE with a Grade 3 or higher	6 (3)
Any G/P related AE with a Grade 3 or higher	0
Any serious AE	7 (4)
Any G/P related serious AE	0
Any AE leading to study discontinuation	2 (1)
Any G/P related AE leading to study discontinuation	1 (1)
Any serious AE leading to study discontinuation	0
Death	0
AEs occurring in ≥10% total patients	
Fatigue	29 (16)
Headache	27 (15)
Laboratory Abnormalities	
ALT, Grade ≥3 (>5 × ULN)	0
AST, Grade ≥3 (>5 × ULN)	0
Total Bilirubin, Grade ≥3 (>3 × ULN)	0

AE, adverse event; DAA, direct-acting antiviral; ALT, alanine aminotransferase; ULN, upper limit of normal.

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CONCLUSIONS

- Eight- or 12-weeks treatment with GLE + PIB or G/P yielded high SVR12 rates in patients with HCV GT5 or GT6 infection without cirrhosis or with compensated cirrhosis. Efficacy was demonstrated in diverse GT6 subtypes (16 GT6 subtypes). In addition, 8-week treatment of patients with compensated cirrhosis achieved high SVR12 (10/10 patients achieved SVR12)
- The GLE + PIB or G/P regimen was well-tolerated, with mostly mild or moderate treatment-emergent adverse events (AEs); no serious AEs were attributed to G/P or led to study drug discontinuation; and no grade 3 or higher ALT, AST or total bilirubin elevation occurred
- The integrated data across 2b, 3a, and 3b studies represent the largest evaluation of patients with HCV GT5 or GT6 infection and the most diverse report of GT6 subtypes to date, supporting the indication of glecaprevir 300 mg and pibrentasvir 120 mg combination as a short duration, pangenotypic regimen

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