Glecaprevir/Pibrentasvir in Patients With Chronic Hepatitis C Virus Infection and Prior Treatment Experience: An Integrated Phase II/III Analysis

THU-296

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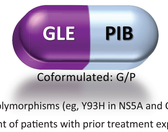
INTRODUCTION

- Anti-hepatitis C virus (HCV) regimens containing direct-acting antivirals (DAAs) are highly effective; however, as more patients are treated with DAAs, the number of patients developing resistance to these DAAs is expected to grow[1]
- Baseline polymorphisms or treatment-emergent resistance-associated substitutions (RASs) are common in patients with virologic failure, allowing for the persistence and potential spread of treatment resistant HCV[1–5]
  - In particular, HCV with NS5A RASs could persist over several years; in contrast, most NS3 RASs disappear within 18 months after NS3/4 protease inhibitor treatment[6,7]
- Many DAA-containing regimens exhibit decreased efficacy in patients with prior virologic failure likely due to decreased potency against RASs, thereby limiting treatment options for this difficult-to-cure population[8–11]
- Glecaprevir (an NS3/4A protease inhibitor identified by AbbVie and Enanta) and pibrentasvir (an NS5A inhibitor) are potent inhibitors that maintain activity against common NS3/4 and NS5A RASs, respectively[12,13]
  - Pibrentasvir maintains activity against most double or triple NS5A RAS combinations tested[12]

G/P is Approved for Patients With Treatment Experience

Glecaprevir
pangenotypic NS3/4A protease inhibitor



Coformulated: G/P

Pibrentasvir
pangenotypic NS5A inhibitor

- Potent against common polymorphisms (eg, Y93H in NS5A and Q80K in NS3)[12,13]
- G/P approved for treatment of patients with prior treatment experience with interferon (with or without ribavirin) or an NS5B inhibitor in US and EU[14,15]
- Also approved for NS5A inhibitor- or NS3/4A protease inhibitor (PI)-experienced, GT1-infected patients in US[14]
- Favorable safety profile irrespective of baseline factors such as compensated liver cirrhosis or advanced renal disease

G/P is orally 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.

- Here we report efficacy and safety of G/P in patients with prior treatment experience who received a US and/or EU label-approved G/P regimen

OBJECTIVE

- Evaluate G/P efficacy and safety in patients with prior treatment experience and eligible for re-treatment based on US and/or EU label-recommended durations and prior HCV treatment

METHODS

- Data for 362 treatment-experienced patients with chronic HCV genotype (GT) 1–6 infections receiving US- and/or EU-approved G/P re-treatment regimen were pooled from ten Phase 2 and 3 registrational studies
  - Studies included SURVEYOR-I and -II, MAGELLAN-1, and ENDURANCE-1, -2, -3, and -4, and EXPEDITION-1, -2, and -4
  - Data were included for all patients who received at least 1 dose of G/P in an intent-to-treat analysis
- A post-hoc analysis was performed of patients with prior treatment experience in clinical trials who received G/P per US and/or EU label recommendations **(Table 1)**

Table 1. G/P Use in Patients With Prior Treatment Experience Based on US- and/or EU-recommended Label*

HCV genotype	Prior Treatment Experience	Without Cirrhosis	With Compensated Cirrhosis
1	NS5A inhibitor without PI†	16 weeks	16 weeks
1	NS3/4A PI without NS5A†	12 weeks	12 weeks
1, 2, 4, 5, 6	PRS	8 weeks	12 weeks
3	PRS	16 weeks	16 weeks

HCV, hepatitis C virus; NS5Ai, non-structural protein 5A inhibitor; NS3/4A PI, non-structural protein 3/4A protease inhibitor; IFN, interferon; RBV, ribavirin; PRS, experienced with interferon (IFN) or pegylated (peg) IFN ± RBV, or sofosbuvir + RBV ± pegIFN.
*EU does not recommend G/P use in GT1-infected patients with prior treatment experience with a regimen containing an NS5A inhibitor or an NS3/4A PI.
†Regimens also could contain pegIFN, SOF, and/or RBV; only recommended per US label.

KEY ELIGIBILITY CRITERIA

- Adults (≥18 years) with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection (HCV RNA >1000 IU/mL)

METHODS (CONTINUED)

- Prior treatment experience with interferon (IFN) or pegylated (peg) IFN ± RBV or sofosbuvir + RBV ± pegIFN for all HCV genotypes or a regimen containing either an NS3/4A PI or an NS5A inhibitor (but not both) for HCV GT1 only
- Body-mass index (BMI) ≥18 kg/m^2
- Compensated liver disease with or without cirrhosis. The presence or absence of cirrhosis was assessed based on liver biopsy, Fibroscan®, or Fibrotest® and APRI
- Absence of co-infection with hepatitis B virus
- Normal renal function or any degree of renal impairment including end-stage renal disease/dialysis

ENDPOINTS AND ANALYSES

- Percentage of patients with SVR12 (HCV RNA <LLOQ 12 weeks after the last dose of study drug) in an intent-to-treat (ITT) analysis
- Adverse events (AEs), including AEs leading to treatment discontinuations, serious AEs, and laboratory abnormalities
- Baseline and treatment-emergent substitutions detected at 15% threshold by next generation sequencing at resistance-associated amino acid positions in NS3 or NS5A

RESULTS

PATIENTS

- Of the 362 patients, most (73%; 264/362) had prior treatment experience with pegIFN + RBV, while 27% (98/362) were DAA-experienced with either SOF + RBV ± pegIFN (15%; 56/362), an NS5A inhibitor (but not NS3/4A PI) (5%; 17/362), or an NS3/4A PI (but not NS5A inhibitor) (7%; 25/362)
- Overall, patients with prior treatment experience were primarily male, white, had GT1 infection, and were without cirrhosis
- Baseline RASs were present in 13% (48/362) of all patients with prior treatment experience, including 1% (5/362) with NS3 and 12% (43/362) with NS5A substitutions

Table 2. Baseline Demographics and Disease Characteristics

Characteristic	pegIFN + RBV alone N = 264	SOF + RBV ± pegIFN N = 56	NS5A inhibitor (w/o PI)* N = 17	NS3/4A PI (w/o NS5Ai)* N = 25	Overall N = 362
Male, n (%)	161 (61)	47 (84)	12 (71)	17 (68)	237 (65)
Race, n (%)					
White	214 (81)	50 (89)	14 (82)	16 (64)	294 (81)
Black or African American	10 (4)	4 (7)	2 (12)	9 (36)	25 (7)
Asian	38 (14)	1 (2)	1 (6)	0	40 (11)
Other	2 (<1)	1 (2)	0	0	3 (<1)
Age, median (range), years	56 (19–84)	60 (47–70)	59 (51–70)	56 (34–67)	57 (19–84)
BMI, median (range), kg/m^2	25.9 (17.3–42.6)	28.6 (21.4–47.9)	29.9 (22.7–38.4)	29.0 (20.9–41.1)	26.7 (17.3–47.9)
Baseline HCV RNA level, median (range), $\log_{10}$ IU/mL	6.2 (3.8–7.4)	6.1 (4.7–7.4)	6.0 (5.1–7.1)	6.5 (4.9–7.2)	6.2 (3.8–7.4)
HCV RNA ≥1 million IU/mL	162 (61)	33 (59)	12 (71)	16 (64)	223 (62)
HCV genotype, n (%)					
GT1	181 (69)	9 (16)	17 (100)	25 (100)	232 (64)
Subtype 1a	61 (23)	5 (9)	13 (76)	20 (80)	99 (27)
Subtype 1b	119 (45)	4 (7)	2 (12)	5 (20)	130 (36)
GT2	22 (8)	12 (21)	0	0	34 (9)
GT3	38 (15)	34 (61)	0	0	73 (20)
GT4-6	23 (8)	1 (2)	0	0	23 (6)
Cirrhosis status, n (%)					
With compensated cirrhosis	64 (24)	37 (66)	3 (18)	7 (28)	111 (31)
Without cirrhosis	200 (76)	19 (34)	14 (82)	18 (72)	251 (69)
HIV co-infection, n (%)	30 (11)	3 (5)	0	0	33 (11)
Presence of baseline substitutions, n (%)†					
NS3/4A only	0	1 (2)	0	4 (16)	5 (1)
NS5A only	25 (10)	7 (13)	10 (67)	1 (4)	43 (13)
Both	0	0	0	0	0
None	224 (90)	47 (85)	6 (38)	20 (80)	297 (86)
Missing	15	1	1	0	17

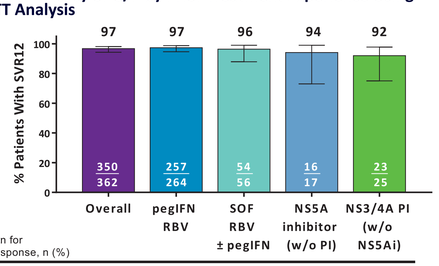
pegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; NS3/4A PI, non-structural protein 3/4A protease inhibitor; NS5AI, non-structural protein 5A inhibitor; BMI, body-mass index; HCV, hepatitis C virus; GT, genotype.
*Regimens also could contain pegIFN, SOF, and/or RBV.
†Amino acid substitutions detected at 15% threshold at positions included in analysis: NS3: 155, 156, 168 for GT1-6. NS5A: 28, 30, 31, 93, H58D, E62A for GT1a; 31, 93 for GT1b; 24, 28, 30, 92, 93 for GT2; 24, 28, 30, 31, 58, 93 for GT3; 24, 28, 30, 31, 93 for GT4; 24, 28, 30, 31, 58, 92, 93 for GT5-6.

RESULTS (CONTINUED)

EFFICACY

- Overall SVR12 rate for the ITT population was 96.7% (95% CI; 94.3–98.1) for patients with prior treatment experience **(Figure 2)**
  - Of the 12 (3%) patients not achieving SVR12, 6 (2%) had on-treatment virologic failure and 3 (<1%) had relapse **(Table 3)**
  - 2 (<1%) patients were lost to follow-up and 1 discontinued early due to serious AEs considered not related to G/P (cerebrovascular accident and cerebral hemorrhage)
- Combined SVR12 rates were ≥95% for all patients with or without cirrhosis **(Figure 3)**
- ITT SVR12 rates examined by various baseline factors were ≥91% **(Figure 4)**

Figure 2. Efficacy of G/P by Prior Treatment Experience Using an ITT Analysis



Reason for non-response, n (%)	Overall	pegIFN RBV	SOF RBV ± pegIFN	NS5A inhibitor (w/o PI)	NS3/4A PI (w/o NS5Ai)
OTVF	3 (0.8%)	2 (0.8%)	0	1 (5.9%)	0
Relapse	6 (1.7%)	4 (1.5%)	2 (3.6%)	0	0
Discontinuation	1 (0.3%)	1 (0.4%)	0	0	0
Lost to follow-up	2 (0.6%)	0	0	0	2 (8.0%)

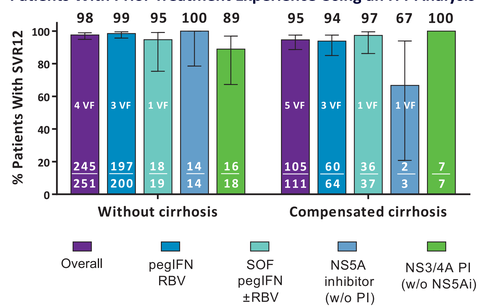
ITT, intent-to-treat; G/P, glecaprevir/pibrentasvir; IFN, interferon; RBV, ribavirin; SOF, sofosbuvir; NS5AI, non-structural protein 5A inhibitor; NS3/4A PI, non-structural protein 3/4A protease inhibitor; OTVF, on-treatment virologic failure.

Table 3. Characteristics of Patients With Virologic Failure

Prior treatment experience	HCV genotype	Cirrhosis; Fibrosis	Reason for non-response	NS3 Substitutions*		NS5A Substitutions*	
				Baseline	Failure	Baseline	Failure
pegIFN + RBV	1a	No; F0–F1	OTVF	None	A156V	None	Q30R + L31M + H58D
pegIFN + RBV	3a	Yes; F4	OTVF†	A166S	A156G + A166S	None	A30K + Y93H
pegIFN + RBV	1a	Yes; F4	Relapse	None	None	Y93N	Q30R, Y93N
pegIFN + RBV	3a	No; F0–F1	Relapse	None	Y56H + D168R	A30K	A30K + Y93H
pegIFN + RBV	3a	Yes; F4	Relapse	A166S	None	None	M28G
pegIFN + RBV	2a	No; F3	Relapse	None	None	L31M	L31M
SOF + RBV	2a	No; F0–F1	Relapse	None	None	L31M	L31M
SOF + RBV	3a	Yes; F4	Relapse	None	None	None	L31F + Y93H
SOF + NS5A inhibitor	1a	Yes; F4	OTVF	None	A156V	Q30R + L31M	Q30R + L31M + H58D

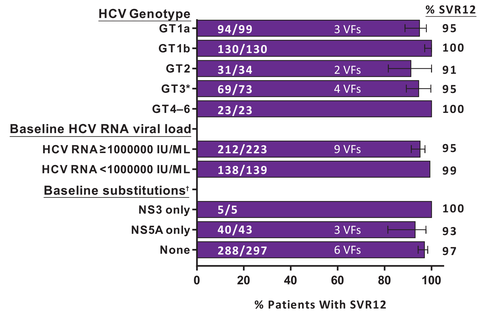
HCV, hepatitis C virus; NS3, non-structural protein 3/4A; NS5A, non-structural protein 5A; IFN, interferon; RBV, ribavirin; OTVF, on-treatment virologic failure; SOF, sofosbuvir.
*Substitutions detected at 15% threshold at amino acid positions included in analysis of patients: 36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3 only), 168 in NS3; 24, 28, 29, 30, 31, 32, 58, 62 (GT1 only), 92, 93 in NS5A. For samples with multiple substitutions within a target, if individual substitutions were detected at ≥90% prevalence, they are considered to be linked and denoted by "+", whereas if one or more of the substitutions was detected at <90% prevalence, they are separated by a comma.
†Patient was not adherent to G/P treatment and had G/P exposures greater than 50% lower than other patients; all other patients with virologic failure were adherent to G/P treatment.

Figure 3. Subgroup Efficacy Analysis of G/P by Cirrhosis Status in Patients With Prior Treatment Experience Using an ITT Analysis



ITT, intent-to-treat; VF, virologic failure including breakthrough or relapse; IFN, interferon; RBV, ribavirin; SOF, sofosbuvir; NS5Ai, non-structural protein 5A inhibitor; NS3/4A PI, non-structural protein 3/4A protease inhibitor.

Figure 4. SVR12 by Disease Characteristics for All Patients With Prior Treatment Experience Treated With G/P Using an ITT Analysis



HCV, hepatitis C virus; GT, genotype; NS3/4A, non-structural protein 3/4A; NS5A, non-structural protein 5A.
*Includes 47 GT3 patients with compensated cirrhosis; 45/47 (95.7%) achieved SVR12.
†Amino acid substitutions detected at 15% threshold at positions included in analysis: NS3: 155, 156, 168 for GT1–6. NS5A: 28, 30, 31, 93, H58D, E62A for GT1a; 31, 93 for GT1b; 24, 28, 30, 92, 93 for GT2; 24, 28, 30, 31, 58, 93 for GT3; 24, 28, 30, 31, 93 for GT4; 24, 28, 30, 31, 58, 92, 93 for GT5–6.

SAFETY

- In the safety analysis (N = 362), G/P was well-tolerated, with no DAA-related serious AEs and few patients experiencing AEs leading to treatment discontinuation (0.6%) and grade ≥3 laboratory abnormalities in total bilirubin (0.8%) with none experiencing concurrent ALT post-nadir grade ≥3 elevations

LIMITATIONS

- Given that this analysis and subgroup analyses were not pre-specified in the respective studies, limitations inherent to the post-hoc nature of this integrated analysis may affect data interpretation
- There were a limited number of patients with NS5A inhibitor (N = 17) or NS3/4A PI (N = 25) experience
- Patients with both NS5A inhibitor and NS3/4A PI experience are not recommended for re-treatment with G/P and thus are not included in this analysis
  - Despite the high barrier for resistance particularly with pibrentasvir, additional data needs to be generated in NS5A inhibitor/PI-experienced patients to confirm the previously-reported efficacy results[16]

CONCLUSIONS

- G/P demonstrated high efficacy in patients with prior treatment experience including in those previously treated with either an NS3/4 PI- or NS5A inhibitor-containing regimen
- Overall, G/P was highly efficacious in patients with prior treatment experience regardless of the type of treatment experience, genotype 1 subtype, baseline viral load, and presence of NS3 or NS5A baseline substitutions
- G/P demonstrated a favorable safety profile with no DAA-related serious AEs, and few AEs leading to treatment discontinuation or grade ≥3 laboratory abnormalities
- Overall, our results demonstrated that G/P is an efficacious and safe re-treatment regimen for patients with prior treatment experience, including those with a regimen containing either NS3/4A PI or NS5A inhibitor (but not both)

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