Time to Viral Suppression Does not Impact SVR in Patients Treated With Glecaprevir/Pibrentasvir for 8 Weeks

THU-384

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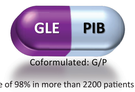
INTRODUCTION

- The pangenotypic direct-acting antivirals (DAAs) glecaprevir coformulated with pibrentasvir (G/P) are approved to treat chronic HCV infection for all 6 major genotypes (GT)

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

Glecaprevir pangenotypic NS3/4A protease inhibitor



Pibrentasvir pangenotypic NS5A inhibitor

- Pangenotypic SVR12 rate of 98% in more than 2200 patients
- Potent against common polymorphisms (eg, Y93H in NS5A and Q80K in NS3)
- Favorable safety profile irrespective of baseline factors such as compensated liver cirrhosis and advanced renal disease
- 8 week duration approved for all treatment-naïve patients without cirrhosis[1]

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.

- Response Guided Therapy based on treatment Week 4 (TW4) HCV RNA was widely used by clinicians in the interferon (IFN) era to determine whether treatment with first generation DAAs should be extended in order to prevent relapse
- With the broadened use of shortened 8-week DAA regimens, concerns remain that failure to suppress HCV RNA quickly may lead to relapse
- AASLD guidelines state the significance of quantifiable HCV RNA at TW4 is unknown and provide no recommendations for stopping or extending therapy[2]

OBJECTIVES

Investigate whether lack of viral suppression by TW4 is predictive of relapse in patients receiving G/P for 8 weeks, and evaluate factors impacting time to viral suppression.

METHODS

- Data were pooled from five phase 2 or 3 clinical studies and included patients who received G/P (300 mg/120 mg) once-daily for 8 weeks
- Patients lost to follow up or with missing SVR12 data (N = 13) were excluded from the analysis since the impact of viral suppression on response cannot be assessed in these patients
- Since we sought to determine whether quantifiable HCV RNA at TW4 was predictive of relapse, 2 patients with on-treatment virologic failure were excluded:
  - GT1a white male, PR-experienced, F0-1 fibrosis, with baseline viral load of 5.4 M IU/mL failed to suppress with TW2 nadir of 139 IU/mL and rebound at TW4 to 1860 IU/mL
  - GT3a white male, naïve, F3 fibrosis, with baseline viral load of 7.7 M IU/mL failed to suppress with TW4 nadir of 37 IU/mL and rebound at TW8 to 7200 IU/mL; this patient was non-compliant

KEY ELIGIBILITY CRITERIA

- Chronic HCV GT 1–6 infection without cirrhosis
- Treatment-naïve or experienced with IFN or pegIFN ± ribavirin (RBV) or sofosbuvir + RBV ± pegIFN

METHODS (CONTINUED)

ENDPOINTS AND ANALYSES

Primary Analysis	Viral suppression, defined as HCV RNA below the lower limit of quantification (LLOQ*) at treatment Week 4 (TW4)
Efficacy Endpoint	The primary endpoint of the individual studies was HCV RNA <LLOQ 12 weeks post-treatment (SVR12)
Logistic Regression	A stepwise multivariate logistic regression analysis assessed the association between HCV RNA >LLOQ at TW4 and select baseline characteristics:

Sex (Male/Female)	Baseline APRI
Age (Year)	Concomitant PPI use (Yes, No)
BMI (kg/m^2)	On Opioid Agonist Therapy (Yes, No)
Race (Black, Non-black)	Injection Drug Use (Yes, No)
Ethnicity (Hispanic or Latino, Not Hispanic or Latino)	Baseline RAS (NS3 only, NS5A only, NS3 + NS5A, None)
IL28B Genotype (CC, Non-CC)	HCV Treatment History (Naive, Experienced)
Genotype (1,2,3,4,5,6)	HIV Coinfection (Yes, No)
Baseline HCV RNA ($\log_{10}$/mL)	DAA Adherence (Yes, No)
Baseline fibrosis stage (F0–F1, F2, F3)	

*Due to assay differences, LLOQ for the SURVEYOR-I and –II studies was 25 IU/mL (Roche COBAS TaqMan® RT-PCR assay v. 2.0) and LLOQ for the ENDURANCE-1, ENDURANCE-3, and EXPEDITION-2 studies was 15 IU/mL (Roche COBAS Ampliprep/TaqMan® RT-PCR assay v. 2.0).

RESULTS

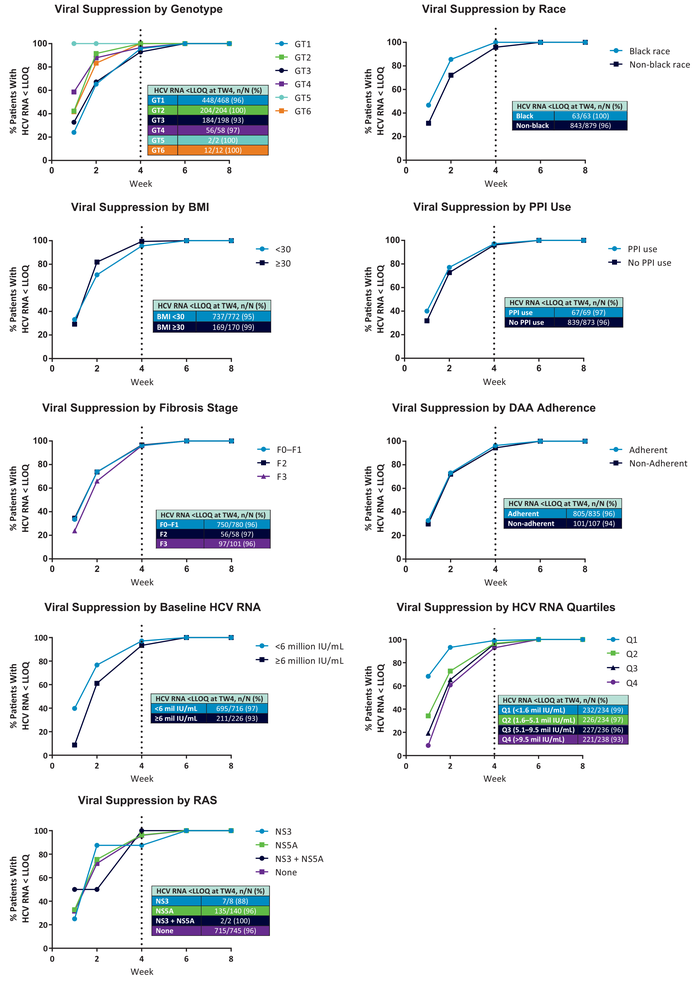
Table 1. Baseline Demographics and Disease Characteristics

Characteristic	8-week G/P N = 950
Male, n (%)	526 (55)
White race, n (%)	783 (82)
Black race, n (%)	63 (7)
Age, mean (range), years	50 (19–84)
BMI, mean (range), kg/m^2	26.3 (17.3–65.7)
Genotype, n (%)	
1a/1b/1 other	240 (25)/229 (24)/1 (<1)
2	204 (21)
3	203 (21)
4/5/6	59 (6)/2 (<1)/12 (1)
Treatment-experienced, n (%)	196 (21)
IFN or pegIFN ± RBV	186 (20)
SOF + RBV ± pegIFN	10 (1)
HCV RNA, median (Q1–Q3), IU/mL	1 680 000 (412 000–5 610 000)
Fibrosis stage, n (%)	
F0–F1	787 (83)
F2	58 (6)
F3	102 (11)
HIV-1 coinfection, n (%)	151 (16)
History of IDU, n (%)	417 (44)
DAA adherent*, n (%)	839 (88)
Concomitant PPI use, n (%)	70 (7)
Presence of baseline polymorphisms†, n (%)	
NS3/4A only	8 (1)
NS5A only	141 (16)
NS3/4A and NS5A	2 (<1)
None	752 (83)

G/P, glecaprevir/pibrentasvir; BMI, body mass index; HCV, hepatitis C virus; pegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; HIV, human immunodeficiency virus; IDU, injection drug use; DAA, direct-acting antiviral; PPI, proton pump inhibitor.
*DAA adherence calculated as the percentage of tablets taken relative to the total expected number of tablets, and must be between 80% and 120% at each 4-week dispensation interval; adherence values below 80% and above 120% were considered non-adherent.
†The detection threshold was 15%. NS3 resistance-associated substitution (RAS) positions included in this analysis were 155, 156 and 168. NS5A RAS positions included in this analysis were 24, 28, 30, 31, 32, 58, 92, and 93.

RESULTS (CONTINUED)

Figure 1. Percentage of Patients With Viral Suppression Over Time by Patient Subgroup



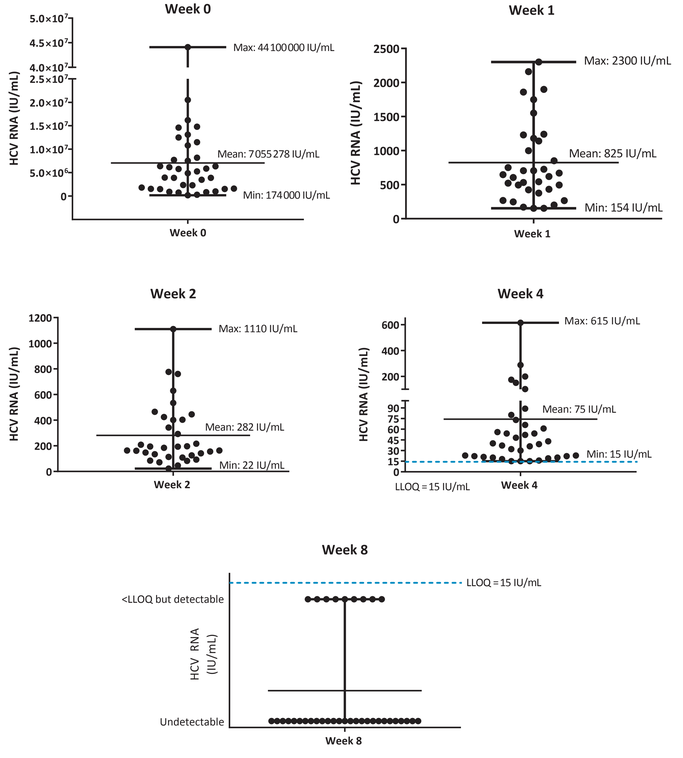
LOGISTIC REGRESSION ANALYSIS

- Of the 17 baseline factors analyzed, 16 had no impact on reaching viral suppression at TW4
  - Baseline HCV RNA was associated with having quantifiable HCV RNA at TW4 (odds ratio = 2.676 [95% CI 1.5–4.7], *P*-value <.001)
    - A separate logistic regression analysis showed that baseline HCV RNA was not associated with achievement of SVR12[3]

EFFICACY

- 99% SVR12 in 943/950 GT1–6 patients treated with G/P for 8 weeks
  - All patients with relapse had unquantifiable HCV RNA at TW4
- TW4 data was available for 942/950 patients:
  - 96% (906/942) of patients had unquantifiable HCV RNA at TW4 **(Figure 1)**
    - 99% achieved SVR12
  - 4% (36/942) of patients had quantifiable HCV RNA at TW4 **(Figure 2)**
    - 100% (36/36, 95% CI 90.4–100.0) achieved SVR12
  - 24% (223/942) had detectable HCV RNA at TW4
    - 97% (217/223) achieved SVR12 (95% CI 94.3–98.8)
    - 6 patients relapsed; 2 had GT2 infection and 4 had GT3 infection
- An analysis of patients treated with 12-week G/P in Phase 3 studies assessed whether patients with detectable HCV RNA at TW4 had similar SVR rates as those treated for 8 weeks:
  - 29% (260/893) of patients treated with G/P for 12 weeks had detectable HCV RNA at TW4
    - >99% (259/260) achieved SVR12 (95% CI 97.9–99.9)
    - There was no statistical difference between the 8- and 12-week SVR rates among patients with detectable HCV RNA at TW4

Figure 2. Viral Load Distribution by Treatment Visit for Patients with Quantifiable HCV RNA at TW4



HCV RNA at baseline and treatment Week 1, 2, 4, and 8 is shown for 36 patients with quantifiable HCV RNA at TW4. Error bars represent the mean (range).

CONCLUSIONS

- Time to viral suppression did not impact efficacy in patients treated with G/P for 8 weeks
- 4% of patients treated with 8-week G/P had quantifiable HCV RNA at TW4, and all achieved SVR12
- Of the 17 variables assessed by multivariate logistic regression, only baseline viral load was associated with having quantifiable HCV RNA at TW4
- In published real-world data of patients receiving 8-week ledipasvir/sofosbuvir, 27% or 68% of patients had quantifiable or detectable HCV RNA at TW4, respectively; SVR12 (mITT) in this population was 97%[4]
- Taken together, these data suggest that treatment extension in patients eligible for 8-week regimens is not warranted based on TW4 viral loads

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DISCLOSURES

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