

## 2.0 Synopsis

<b>AbbVie Inc.</b>	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Glecaprevir (GLE)/ Pibrentasvir (PIB)		
<b>Name of Active Ingredient:</b> GLE/PIB		
<b>Title of Study:</b> A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection		
<b>Investigator:</b> [REDACTED] MD		
<b>Study Sites:</b> 14 sites in Brazil		
<b>Publications:</b> None		
<b>Studied Period (Years):</b> First Subject First Visit: 06 June 2018 Last Subject Last Visit: 11 March 2019	<b>Phase of Development:</b> 3b	
<p><b>Objective:</b></p> <p>The primary objective of this study was to assess the efficacy by evaluating the percentage of subjects achieving sustained virologic response 12 weeks postdosing (SVR<sub>12</sub>) (HCV ribonucleic acid [RNA] &lt; lower limit of quantification [LLOQ] 12 weeks following therapy) and the safety of the GLE/PIB combination in treatment-naïve (TN) adults in Brazil with chronic HCV GT1 – GT6 infection without cirrhosis or with compensated cirrhosis. The efficacy and safety endpoints were analyzed on the overall population (i.e., across treatment durations and genotypes).</p>		
<p><b>Methodology:</b></p> <p>Study M16-156 was a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB for an 8- or 12- week treatment duration in adults in Brazil with chronic HCV GT1 – GT6 infection, without cirrhosis or with compensated cirrhosis with a METAVIR System Fibrosis Score of F2, F3, or F4 (F2-F4) or equivalent, who were HCV TN.</p> <p>The study consisted of a Screening Period, a Treatment Period, and a Post-Treatment (PT) Period. Safety and efficacy were assessed throughout the study. In the PT Period, all subjects administered at least 1 dose of study drug were monitored for 12 weeks following the last dose of study drug for safety, HCV ribonucleic acid, and the emergence and/or persistence of resistance-associated viral variants. The planned total duration of the study (excluding screening) was up to 24 weeks for all subjects.</p>		
<p><b>Number of Subjects (Planned and Analyzed):</b></p> <p>Planned: 1) a minimum of approximately 35 GT1 and approximately 25 GT3 subjects and 2) approximately 80 F2-F3 and a maximum of approximately 20 F4 subjects.</p> <p>Analyzed: 100 subjects (75 HCV GT1 – 6 without cirrhosis [F2-F3] treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks and 25 HCV GT1 – GT6 subjects with compensated cirrhosis (F4) treated with GLE/PIB 300 mg/120 mg QD for 12 weeks).</p>		

**Diagnosis and Main Criteria for Inclusion:**

**Key Inclusion Criteria:**

- Male or female, at least 18 years of age at time of Screening.
- Females of childbearing potential must have had a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1. Females of non-childbearing potential at Screening did not require pregnancy testing.
- Screening laboratory result indicating HCV GT1-, 2-, 3-, 4-, 5- and/or 6-infection. Mixed and indeterminate genotypes were acceptable.
- Subject had positive plasma HCV antibody and HCV RNA viral load  $\geq 1000$  international units (IU)/mL at Screening Visit.
- Subject must have been documented as without cirrhosis (METAVIR equivalent fibrosis stage of F2 – F3), or with compensated cirrhosis (METAVIR equivalent fibrosis stage of F4 with a Child-Pugh score of  $\leq 6$ ).
- Subjects with compensated cirrhosis only: Absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative ultrasound at Screening. Subjects who had an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver were eligible for the study.
- Subjects who were known to be HCV/human immunodeficiency virus (HIV) co-infected may have enrolled if they had a positive test result for anti-HIV antibody at Screening and were: naïve to treatment with any antiretroviral therapy (ART), or on a stable, qualifying ART regimen for at least 8 weeks prior to Baseline.

**Key Exclusion Criteria:**

A subject was not eligible for study participation if he/she met any of the following criteria:

- Female subject who was pregnant, breastfeeding or was considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
- Current hepatitis B virus (HBV) infection on screening tests, defined as:
  - A positive hepatitis B surface antigen (HBsAg), or;
  - HBV deoxyribonucleic acid (DNA)  $>$  LLOQ in subjects with isolated positive anti-hepatitis B core antibody (anti-HBc) (i.e., with negative HBsAg and anti-hepatitis B surface antigen [anti-HBs])
- Any current or past clinical evidence of Child-Pugh B or C classification (score of  $> 6$ ) or any current or past clinical history of liver decompensation including ascites on physical exam, hepatic encephalopathy or variceal bleeding. Prophylactic use of beta blockers was not exclusionary.

<p><b>Diagnosis and Main Criteria for Inclusion (Continued):</b></p> <p><b>Key Exclusion Criteria (Continued):</b></p> <ul style="list-style-type: none"> <li>• Laboratory parameters exclusions: <ul style="list-style-type: none"> <li>○ Alanine aminotransferase (ALT) &gt; 10 × upper limit of normal (ULN); aspartate amino transferase (AST) &gt; 10 × ULN</li> <li>○ Total bilirubin &gt; 3.0 mg/dL</li> <li>○ Albumin &lt; lower limit of normal (LLN) (without cirrhosis); &lt; 2.8 mg/dL (with compensated cirrhosis)</li> <li>○ Platelets &lt; 90,000 10<sup>3</sup>/μL (without cirrhosis); &lt; 60,000 10<sup>3</sup>/μL (with compensated cirrhosis)</li> </ul> </li> <li>• History of solid organ transplantation, unless the implanted organ had since been removed, or was non-functional, and subject was no longer on immunosuppressive medication. If the organ was non-functional, the subject must have been clinically stable off of immunosuppressive medication for a minimum of 6 months prior to Screening.</li> <li>• Receipt of any investigational or commercially available anti-HCV agents, including, but not limited to: interferon, pegylated interferon, ribavirin, sofosbuvir, telaprevir, boceprevir, SMV, asunaprevir, veruprevir, glecaprevir, grazoprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, voxilaprevir, velpatasvir, pibrentasvir, or dasabuvir.</li> </ul>																				
<p><b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b></p> <table border="1"> <thead> <tr> <th>Investigational Product</th> <th>Manufacturer</th> <th>Mode of Administration</th> <th>Dosage Form</th> <th>Strength</th> <th>Bulk Lot Number</th> </tr> </thead> <tbody> <tr> <td rowspan="2">GLE/PIB</td> <td rowspan="2">AbbVie</td> <td rowspan="2">Oral</td> <td>Film-coated</td> <td>100 mg/</td> <td>16-001002</td> </tr> <tr> <td>Tablet</td> <td>40 mg</td> <td>16-005216</td> </tr> </tbody> </table>						Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number	GLE/PIB	AbbVie	Oral	Film-coated	100 mg/	16-001002	Tablet	40 mg	16-005216
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<p><b>Duration of Treatment:</b></p> <p>Subjects received GLE/PIB 300 mg/120 mg once daily (QD) for 8 or 12 weeks depending on their cirrhosis status.</p>																				
<p><b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b></p> <p>Not applicable</p>																				
<p><b>Criteria for Evaluation</b></p> <p><b>Efficacy:</b></p> <p>The primary efficacy variable was the percentage of subjects who achieved SVR<sub>12</sub> (HCV RNA &lt; LLOQ 12 weeks after the last actual dose of study drug).</p> <p>The secondary efficacy variables were:</p> <ul style="list-style-type: none"> <li>• The percentage of subjects with HCV on-treatment virologic failure (OTVF).</li> <li>• The percentage of subjects with HCV virologic relapse.</li> </ul>																				

### Criteria for Evaluation (Continued)

#### Resistance:

For all subjects who received GLE/PIB, the variants at signature resistance-associated amino acid positions at baseline were identified by next-generation sequencing (NGS) based on comparison to the appropriate prototypic reference sequence.

The following resistance information was analyzed for subjects who received GLE/PIB, who did not achieve SVR<sub>12</sub>, and who had a post-baseline sample with HCV RNA  $\geq$  1,000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequence, 2) the amino acid substitutions in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral resistance by NGS.

#### Pharmacokinetic:

Plasma concentrations for GLE and PIB were tabulated and summarized for each subject.

#### Safety:

Safety and tolerability were assessed by monitoring adverse events (AEs), physical examinations, clinical laboratory tests, and vital signs.

### Statistical Methods

#### Efficacy:

The primary efficacy endpoint was the percentage of subjects who achieved SVR<sub>12</sub> (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) across all genotypes (GT1 – 6) on combined treatment groups, based on the intention-to-treat (ITT) population. The number and percentage of subjects achieving SVR<sub>12</sub> were calculated along with a two-sided 95% confidence interval (CI) using the Wilson's score method.

A summary of the reasons for SVR<sub>12</sub> non-response (e.g., OTVF, relapse, other) was provided.

The following secondary efficacy endpoints were summarized for the ITT population:

- The percentage of subjects with HCV OTVF.
- The percentage of subjects with HCV relapse.

#### Resistance:

The genes of interest for NGS in this study in all samples were those encoding full length nonstructural viral protein 3/4A (NS3/4A) and nonstructural viral protein 5A (NS5A). The following resistance analyses were conducted: 1) baseline polymorphisms at signature amino acid positions (as well as a key subset of amino acid positions) at baseline identified by NGS at 2% or 15% detection thresholds were compared to the appropriate prototypic reference sequence and 2) a comparison of sustained virologic response rates for subjects with and without baseline variants at the positions of interest in nonstructural viral protein 3 (NS3) and NS5A was provided. For subjects experiencing virologic failure, sequences at available postbaseline timepoints were compared to baseline and appropriate prototypic reference sequences to identify treatment-emergent substitutions.

#### HCV Genotype/Subtype:

Phylogenetic analysis was conducted on all available HCV sequences from baseline samples in order to accurately determine HCV subtype.

**Statistical Methods (Continued)**

**Subgroup:**

The percentage of subjects with SVR<sub>12</sub> was calculated, along with the corresponding 2-sided 95% Wilson score intervals, for subgroup variables such as HCV genotype and available subtype and baseline HCV RNA level.

**Pharmacokinetics:**

Plasma concentrations of GLE and PIB were tabulated for each subject. Summary statistics were computed for GLE and PIB plasma concentrations binned by time since last dose.

**Safety:**

All subjects who received at least 1 dose of study drug were included in the safety analyses. The number and percentage of subjects with treatment-emergent AEs (i.e., any event that began or worsened in severity after initiation of study drug through 30 days after the last dose of study drug) were tabulated by primary Medical Dictionary for Regulatory Activities® v21.1 system organ class and preferred term. The tabulation of the number of subjects with treatment-emergent AEs by severity grade (Grades 1 – 5) and relationship to study drug was also provided.

Changes in clinical laboratory and vital sign data from baseline to each postbaseline visit were summarized descriptively. The number and percentage of subjects with postbaseline laboratory values during the Treatment Period meeting toxicity grades and meeting potential hepatotoxicity criteria were tabulated. The number and percentage of subjects with postbaseline values during the Treatment Period meeting prespecified criteria for potentially clinically significant vital sign values were tabulated.

**Summary/Conclusions**

**Efficacy Results:**

SVR<sub>12</sub> was achieved in 98.0% (98/100, 95% CI: 93.0%, 99.4%) of subjects in the ITT population. Two GT3-infected subjects did not achieve SVR<sub>12</sub>, 1 due to relapse and 1 due to missing SVR<sub>12</sub> data.

**Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR<sub>12</sub>) (ITT Population)**

Assessment	All Subjects N = 100
SVR <sub>12</sub> , n/N (%)	98/100 (98.0)
2-sided 95% CI <sup>a</sup>	(93.0, 99.4)
Nonresponse, n/N (%)	2/100 (2.0)
Reason for nonresponse, n/N (%)	
Virologic failure	1/100 (1.0)
On-treatment virologic failure	0/100
Breakthrough	0/100
End-of-treatment failure	0/100
Relapse <sub>12</sub>	1/100 (1.0)
Non-virologic failure	1/100 (1.0)
Premature study drug discontinuation	0/100
HCV reinfection	0/100
Missing SVR <sub>12</sub> data	1/100 (1.0)
Other	0/100

CI = confidence interval; GLE/PIB = glecaprevir/pibrentasvir; HCV = hepatitis C virus; ITT = intention-to-treat; QD = once daily; Relapse<sub>12</sub> = virologic relapse by Post-Treatment Week 12; RNA = ribonucleic acid; SVR = sustained virologic response; SVR<sub>12</sub> = sustained virologic response 12 weeks postdosing

a. Calculated using the Wilson score method.

Notes: GLE/PIB 300 mg/120 mg QD for 8 weeks (subjects without cirrhosis) or 12 weeks (subjects with compensated cirrhosis).

Backward imputation, where applicable, was used to impute missing data. After applying backward imputation, if there was still no value in the window but there was an HCV RNA from a local laboratory present, then it was to be imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

**Summary/Conclusions (Continued)**

**Resistance Results:**

Baseline polymorphisms in NS3 (at positions 155, 156, or 168) were not detected in GT1 and GT2-infected subjects and were detected in 2.7% (1/37) of the GT3a-infected subjects. Baseline polymorphisms in NS5A (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 17.9% (10/56), 100% (5/5), and 28.2% (11/39) of the GT1-, GT2-, and GT3-infected subjects, respectively. Baseline polymorphisms in NS3 and/or NS5A did not have an impact on treatment outcome for GT1, 2, and 3-infected subjects.

One GT3a-infected subject experienced virologic failure. This subject did not have baseline polymorphisms in NS3 and had A30K in NS5A at baseline and treatment-emergent Y93H at the time of failure; NS3 sequence was not available for analysis at the time of failure.

**Pharmacokinetic Results:**

Following administration of GLE/PIB 300 mg/120 mg in Brazilian adults with chronic HCV GT1 – GT6 infection, the binned median trough concentration (C22-26) of GLE was about 2-fold and PIB was similar in subjects with compensated cirrhosis when compared to subjects without cirrhosis.

**Safety Results:**

The majority of subjects who experienced AEs had events that were at most Grade 1 in severity, with the most common ( $\geq 10.0\%$  of subjects) being headache (18.0%). Four subjects experienced 6 treatment-emergent SAEs, none of which was assessed as related to study drug or led to treatment discontinuation. No subjects had an AE leading to premature discontinuation of study drug. There were no cases of drug-induced liver injury, hepatic decompensation, HCC, or death.

**Overall Conclusions:**

The fixed-dose combination of GLE/PIB 300 mg/120 mg QD demonstrated high efficacy and a favorable safety profile in TN Brazilian subjects. No safety signal was observed in this study.