2.0 Synopsis

<table>
<thead>
<tr>
<th>AbbVie Inc.</th>
<th>Individual Study Table Referring to Part of Dossier: (For National Authority Use Only)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of Study Drug:</strong></td>
<td>Glecaprevir (GLE; ABT-493)/Pibrentasvir (PIB, ABT-530)</td>
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<tr>
<td><strong>Name of Active Ingredient:</strong></td>
<td>GLE/PIB</td>
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<tr>
<td><strong>Title of Study:</strong></td>
<td>A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Adults with Chronic Hepatitis C Virus (HCV) Genotype 5 or 6 Infection</td>
</tr>
<tr>
<td><strong>Coordinating Investigator:</strong></td>
<td>[Redacted]</td>
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<tr>
<td><strong>Study Sites:</strong></td>
<td>24 sites in Australia, Belgium, Canada, France, New Zealand, Singapore, South Africa, United States, and Vietnam</td>
</tr>
<tr>
<td><strong>Publications:</strong></td>
<td>2 articles and 3 abstracts</td>
</tr>
<tr>
<td><strong>Studied Period (Years):</strong></td>
<td>First Subject First Visit: 25 January 2017; Last Subject Last Visit: 29 August 2018</td>
</tr>
<tr>
<td><strong>Phase of Development:</strong></td>
<td>3b</td>
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**Objectives:**
The primary objective of this study was to assess the efficacy (by evaluating the percentage of subjects achieving SVR\(_{12}\) (HCV ribonucleic acid [RNA] < lower limit of quantification [LLOQ] 12 weeks following therapy) and safety of GLE/PIB in adults with chronic HCV genotype (GT) 5- or GT6-infection, without cirrhosis or with compensated cirrhosis.
The secondary objectives were to assess the percentage of subjects with HCV on-treatment virologic failure and the percentage of subjects with virologic relapse by Post-Treatment (PT) Week 12 (Relapse\(_{12}\)).
Additional objectives were to assess pharmacokinetics and emergence and persistence of viral variants.

**Methodology:**
This was a Phase 3b, open-label, multicenter study evaluating the efficacy and safety of GLE/PIB in adults with chronic HCV GT5 or GT6 infection, without cirrhosis (F0-F3) or with compensated cirrhosis (F4), who were either treatment-naïve or treatment-experienced with interferon (IFN) or pegylated interferon (pegIFN) with or without ribavirin (RBV) or treatment-experienced with sofosbuvir (SOF) plus RBV with or without pegIFN.
Eligible HCV GT5- or GT6-infected non-cirrhotic subjects were treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks, and those with compensated cirrhosis were treated with GLE/PIB 300 mg/120 mg QD for 12 weeks.
Safety and efficacy were assessed by AbbVie throughout the study.
In the PT Period, all subjects administered at least 1 dose of study drug were followed for 24 weeks PT to monitor for safety, HCV RNA, and the emergence and/or persistence of resistance-associated viral variants.
**Methodology (Continued):**
The planned total duration of the study (excluding screening) was up to 36 weeks for all subjects.

**Number of Subjects (Planned and Analyzed):**
Planned: approximately 80 subjects.
Analyzed: 84 subjects were enrolled and received at least 1 dose of study drug.

**Diagnosis and Main Criteria for Inclusion:**

**Main Inclusion Criteria:**
- Male or female (either postmenopausal or permanently surgically sterile, or women of child-bearing potential practicing at least 1 protocol-specified method of birth control on or prior to Study Day 1 through at least 30 days after the last dose of study drug) at least 18 years of age at time of screening.
- Screening laboratory result indicating HCV GT5 or GT6 infection.
- Chronic HCV infection, defined as 1 of the following:
  - Positive for anti-HCV antibody or HCV RNA at least 6 months before screening, or
  - A liver biopsy consistent with chronic HCV infection, or
  - Abnormal alanine aminotransferase levels for at least 6 months before screening.
- HCV treatment-naive (had never received a single dose of any approved or investigational anti-HCV medication) or treatment-experienced (had failed prior IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN therapy). Previous HCV treatment must have been completed ≥ 2 months prior to screening. Prior HCV treatment with any other approved or investigational medications was not allowed.
- Documented as noncirrhotic or having compensated cirrhosis.

**Main Exclusion Criteria:**
- Female who was pregnant, breastfeeding, or planning to become pregnant during the study or during the 30 days after the last dose of study drug.
- Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could have precluded adherence to the protocol, in the opinion of the investigator.
- Positive test result at screening for hepatitis B surface antigen or anti-human immunodeficiency virus antibody.
- HCV genotyping performed during screening indicated coinfection with more than 1 HCV genotype.
- Any cause of liver disease other than chronic HCV infection.
- Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive GLE/PIB.
- History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

<table>
<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>GLE/PIB</td>
<td>AbbVie</td>
<td>Oral</td>
<td>Film-coated tablet</td>
<td>100 mg/40 mg</td>
<td>15-006595</td>
</tr>
</tbody>
</table>

Duration of Treatment:
Subjects received GLE/PIB 300 mg/120 mg QD for 8 to 12 weeks.

Criteria for Evaluation

Efficacy:
Virologic response was assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 24 weeks after completion of treatment.

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$_{12}$, and who had a post-baseline sample with HCV RNA ≥ 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:
Individual plasma concentrations for GLE and PIB were tabulated and summarized for each subject, by subject's cirrhosis status and for all subjects combined.

Safety:
Safety and tolerability were assessed by monitoring adverse events (AEs), physical examinations, clinical laboratory tests, 12-lead electrocardiograms, and vital signs.

Statistical Methods

Efficacy:
The primary efficacy endpoint was SVR$_{12}$ in the intention-to-treat (ITT) population. The number and percentage of subjects achieving SVR$_{12}$ were summarized by HCV genotype (GT5 and GT6) across treatment arms. A two-sided 95% confidence interval (CI) was calculated using the Wilson's score method.

The secondary efficacy endpoints were:
- The percentage of subjects with on-treatment virologic failure (defined as confirmed increase of < 1 log$_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment);
- The percentage of subjects with relapse by PT Week 12 (Relapse$_{12}$), defined as confirmed HCV RNA ≥ LLOQ between the end of treatment and 12 weeks after the last actual dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the final treatment visit, excluding reinfection.
### Statistical Methods (Continued)
#### Efficacy (Continued):
For the analysis of relapse, a subject was considered to have completed treatment if they had a study drug duration of ≥ 52 days for Arm A (subjects without cirrhosis) and ≥ 77 days for Arm B (subjects with compensated cirrhosis). The percentage of subjects meeting each secondary efficacy endpoint was summarized along with 2-sided 95% Wilson score CIs by HCV genotype (GT5 and GT6) across treatment arms.

#### Subgroup:
The percentage of subjects with SVR$_{12}$ in the ITT population was calculated, along with the corresponding 2-sided 95% Wilson score CI by HCV genotype (GT5 and GT6) across treatment arms for subgroup variables such as prior HCV treatment history, type of previous regimen (IFN- or SOF-based) for treatment-experienced subjects, IL28B genotype, and baseline HCV RNA level.

#### Resistance:
The genes of interest for NGS in this study in all samples were those encoding full-length nonstructural viral protein 3/4A and NS5A (NS3/4A, 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 NS3 and NS5A was provided. For subjects experiencing virologic failure, sequences at available post-baseline time points 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 genotype and subtype.

#### Pharmacokinetic:
Individual plasma concentrations and pharmacokinetic parameter values for GLE and PIB were tabulated for each subject, by subject's cirrhosis status and for all subjects combined.

#### 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 (MedDRA®) 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.

Mean changes in clinical laboratory and vital sign data from baseline to each post-baseline visit were summarized descriptively. The number and percentage of subjects with post-baseline laboratory values during the treatment period meeting toxicity grades were summarized, as were subjects meeting criteria for assessment of hepatic laboratory values. The number and percentage of subjects with post-baseline vital sign values during the treatment period meeting pre-specified criteria for potentially clinically significant values were summarized.
Summary/Conclusions

Efficacy Results:

The study population was comprised of 23 subjects infected with HCV GT5a and 61 subjects infected with HCV GT6 (6a: 26 subjects; 6c: 12 subjects; 6l: 4 subjects; 6k and 6n: 3 subject each; 6p: 2 subjects; 6b/6xd, 6c, 6f, 6h, 6j, 6m, 6o, 6q, and 6r: 1 subject each; subtype missing and not available: 1 subject each).

Sustained virologic response 12 weeks post-dosing was achieved in 95.7% (22/23) of HCV GT5-infected subjects and 98.4% (60/61) of HCV GT6-infected subjects in the ITT population. High SVR12 rates were observed regardless of viral or host factors, such as demographics, baseline HCV RNA levels, relevant comorbidities (including cirrhosis status), and prior HCV treatment history.

On-treatment virologic failure was experienced by 1 (1.6%, 95% CI: 0.3%, 8.7%) GT6-infected subject (GT6f, treatment-naïve, with compensated cirrhosis), and Relapse12 was experienced by 1 (4.3%, 95% CI: 0.8%, 21.0%) GT5-infected subject (GT5a, treatment-naïve, without cirrhosis).

High SVR24 rates were observed in HCV GT5 (95.7%, 95% CI: 79.0% to 99.2%) and in HCV GT6-infected subjects (95.1%, 95% CI: 86.5% to 98.3%). Relapse24 was experienced by 1 (1.7%) GT6-infected subject (GT6k, treatment-naïve, without cirrhosis).
Summary/Conclusions (Continued)

Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR$_{12}$) (ITT Population)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>GT5-Infected Subjects</th>
<th>GT6-Infected Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 23</td>
<td>N = 61</td>
</tr>
<tr>
<td>SVR$_{12}$, n/N (%)</td>
<td>22/23 (95.7)</td>
<td>60/61 (98.4)</td>
</tr>
<tr>
<td>2-sided 95% CI$^a$</td>
<td>79.0, 99.2</td>
<td>91.3, 99.7</td>
</tr>
<tr>
<td>Nonresponse, n/N (%)</td>
<td>1/23 (4.3)</td>
<td>1/61 (1.6)</td>
</tr>
<tr>
<td>Reason for nonresponse, n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic failure</td>
<td>1/23 (4.3)</td>
<td>1/61 (1.6)</td>
</tr>
<tr>
<td>On-treatment virologic failure</td>
<td>0/23</td>
<td>1/61 (1.6)</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>0/23</td>
<td>1/61 (1.6)</td>
</tr>
<tr>
<td>End-of-treatment failure</td>
<td>0/23</td>
<td>0/61</td>
</tr>
<tr>
<td>Relapse$_{12}$</td>
<td>1/23 (4.3)</td>
<td>0/60</td>
</tr>
<tr>
<td>Non-virologic failure</td>
<td>0/23</td>
<td>0/61</td>
</tr>
<tr>
<td>Premature study drug discontinuation</td>
<td>0/23</td>
<td>0/61</td>
</tr>
<tr>
<td>HCV reinfection</td>
<td>0/23</td>
<td>0/61</td>
</tr>
<tr>
<td>Missing SVR$_{12}$ data</td>
<td>0/23</td>
<td>0/61</td>
</tr>
<tr>
<td>Other</td>
<td>0/23</td>
<td>0/61</td>
</tr>
</tbody>
</table>

CI = confidence interval; GLE/PIB = glecaprevir/pibrentasvir; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; QD = once daily; Relapse$_{12}$ = virologic relapse by Post-Treatment Week 12; RNA = ribonucleic acid; SVR = sustained virologic response; SVR$_{12}$ = sustained virologic response 12 weeks post-dosing

$^a$ Calculated using the Wilson score method.

Note: 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:
Based on phylogenetic analysis of NS3/4A or NS5A sequences from 83 subjects, the number of subjects infected with each of the following HCV subtypes was: 23 GT5a (27.7%), 26 GT6a (31.3%), 12 GT6e (14.5%), 3 GT6k (3.6%), 4 GT6l (4.8%), 3 GT6n (3.6%), 2 GT6p (2.4%), and 1 each (1.2%) of GT6b/xd, GT6c, GT6f, GT6h, GT6j, GT6m, GT6o, GT6q, and GT6r. Subtype could not be determined on the baseline sample from 1 GT6-infected subject due to lack of homology with any known GT6 subtype.

Baseline polymorphisms at the key subset of amino acid positions in NS3 (at positions 155, 156, or 168) were detected in 56.5% (13/23) and 3.6% (2/56) of the GT5- and GT6-infected subjects, respectively, at 15% detection threshold. NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 13.0% (3/23) and 62.1% (36/58) of the GT5- and GT6 infected subjects, respectively, at 15% detection threshold. The presence of baseline polymorphisms had no impact on treatment outcome in subjects infected with any HCV subtype in this study.

The GT5a-infected subject experiencing virologic failure (Relapse) had NS3-D168E at baseline and at the time of failure, but had no other treatment-emergent substitutions in NS3 or NS5A. The GT6f-infected subject experiencing virologic failure (on-treatment breakthrough) did not have baseline polymorphisms in NS3 or NS5A, and had treatment-emergent substitutions A156M in NS3 and T93A in NS5A at the time of failure; at PT Week 24, NS3-A156M and NS5A-T93A were not detectable, however, L31F in NS5A was detected at this time point. The GT6k-infected subject who achieved SVR but failed to achieve SVR24 did not have baseline polymorphisms or treatment-emergent substitutions in NS5A; NS3 sequences were not available for analysis.

Pharmacokinetic Results:
The binned median trough concentration (C_{22-26}) was 2.4-fold higher for GLE and similar for PIB in adults with chronic HCV GT5 or GT6 infection with compensated cirrhosis when compared to adults with chronic HCV GT5 or GT6 infection without cirrhosis.

Safety Results:
The majority of subjects experienced at least 1 AE during the Treatment Period. Most subjects who experienced AEs had events with a maximum severity of Grade 1 (mild) or Grade 2 (moderate). The most frequently reported (≥ 10.0% of subjects) AEs were fatigue and headache. No deaths were reported. Five subjects (6.0%) experienced 1 or more serious AEs, all considered by the investigator to be not related to study drug. No subjects had an AE leading to premature discontinuation of study drug. No treatment-emergent hepatic decompensation/hepatic failure events (using the AbbVie Product MedDRA Query) or post-baseline events of hepatocellular carcinoma were identified. One subject had a Grade 3 decreased hemoglobin value associated with a serious AE of anemia due to *Helicobacter pylori* gastric ulcer (requiring hospitalization, considered by the investigator to be not related to study drug). No subject had clinically relevant Grade 3/4 chemistry values that worsened compared with baseline during the Treatment Period. No subject met the criteria for the hepatic laboratory abnormalities of interest.

No clinically meaningful observations were noted for vital signs or 12-lead electrocardiogram assessments.
Summary/Conclusions (Continued)
Discussion and Overall Conclusions:

- Study subjects infected with HCV GT5 achieved an SVR$_{12}$ rate of 95.7%, with 1 virologic failure, and study subjects infected with HCV GT6 achieved an SVR$_{12}$ rate of 98.4%, with 1 virologic failure.
- High SVR$_{12}$ rates were observed in HCV GT5- and HCV GT6-infected subjects, regardless of viral or host factors, including demographics, baseline HCV RNA levels, relevant comorbidities (including cirrhosis status), and prior treatment history.
- High SVR$_{24}$ rates were observed in HCV GT5 (95.7%, 95% CI: 79.0% to 99.2%) and in HCV GT6-infected subjects (95.1%, 95% CI: 86.5% to 98.3%). One subject infected with HCV GT6 failed to achieve SVR$_{24}$ due to relapse (Relapse$_{24}$).
- The efficacy results of this study are consistent with and extend the results of studies in the registration program.
- The SVR$_{12}$ and SVR$_{24}$ data from this study provide additional supportive evidence of the label-recommended GLE/PIB regimens for treating patients with HCV GT5 or GT6 infection in a wider geographic region, compared with prior studies, and for diverse subtypes of GT6 HCV infection.
- The binned median trough concentration (C$_{22-26}$) was 2.4-fold higher for GLE and similar for PIB in adults with chronic HCV GT5 or GT6 infection with compensated cirrhosis when compared to adults with chronic HCV GT5 or GT6 infection without cirrhosis.
- The fixed-dose combination of GLE/PIB 300 mg/120 mg QD demonstrated a favorable safety profile. No safety signal was observed in this study.