2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Glecaprevir/Pibrentasvir		
Name of Active Ingredient: Glecaprevir/Pibrentasvir		

Title of Study: A Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 - 6 Infection and Compensated Cirrhosis

Coordinating Investigator: [redacted]

Study Sites: 94 sites in the United States (and its territory, Puerto Rico), Bulgaria, Canada, Czech Republic, France, Greece, Hungary, Ireland, Israel, Italy, Poland, Portugal, Romania, Russia, Spain, Taiwan, United Kingdom, and Vietnam.

Publications: 4

Studied Period (Years): First Subject First Visit: 28 April 2017 Last Subject Last Visit: 08 November 2019	**Phase of Development:** 3b

Objectives:

The primary objectives of this study were to demonstrate the efficacy of the sustained virologic response 12 weeks postdosing (SVR_{12}) rate of 8 weeks of treatment with GLE/PIB compared to the historical SVR_{12} rates of 12 weeks of treatment with GLE/PIB and to assess the safety of 8 weeks of treatment with GLE/PIB in treatment-naïve adults with chronic HCV infection and compensated cirrhosis.

The secondary objectives of this study were to assess the percentage of subjects with on-treatment virologic failure and to assess the percentage of subjects with post-treatment relapse.

Methodology:

This was a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of 8 weeks of GLE/PIB in HCV treatment-naïve adult subjects with chronic HCV infection and compensated cirrhosis.

Safety and efficacy were assessed throughout the study. As this was an open-label study, the safety data were reviewed by AbbVie during the Treatment Period of the study.

In the Post-Treatment Period, all subjects administered at least 1 dose of study drug were monitored for 24 weeks following the last dose of study drug for safety, HCV ribonucleic acid (RNA), and the emergence and/or persistence of resistance-associated viral variants.

The planned total duration of the study (excluding screening) was up to 32 weeks for all subjects.

Number of Subjects (Planned and Analyzed):

Planned: approximately 330 subjects (270 with HCV GT1, GT2, GT4, GT5, or GT6 infection and 60 with HCV GT3 infection).

Analyzed: 343 subjects (280 with HCV GT1, GT2, GT4, GT5, or GT6 infection and 63 with GT3 infection) were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

- Male or female, at least 18 years of age at time of screening.
- Screening central laboratory result indicating HCV GT1 – GT6 infection.
- Subject had a positive plasma antibody (Ab) and HCV RNA viral load ≥ 1,000 IU/mL at screening.
- Subject must have been HCV treatment naïve (i.e., has never received a single dose of any approved or investigational anti-HCV medication).
- Subjects must have been documented as cirrhotic, with Child-Pugh score ≤ 6.

Main Exclusion Criteria:

- Female subject who was pregnant, breastfeeding, or considering becoming pregnant during the study, or for approximately 30 days after the last dose of study drug.
- Hepatitis C virus genotyping performed by the central laboratory during screening indicated coinfection with more than 1 HCV genotype.
- Current hepatitis B virus (HBV) or human immunodeficiency virus (HIV) infection on screening test, defined as:
    - Positive hepatitis B surface antigen (HBsAg), or;
    - HBV deoxyribonucleic acid > lower limit of quantification (LLOQ) in subjects with isolated positive antibody to hepatitis B core antigen (anti-HBc) (i.e., negative HBsAg and anti-hepatitis B), or;
    - Positive anti-HIV Ab
- Any current or historical clinical evidence of decompensated cirrhosis, including any current or past evidence of Child-Pugh B or C classification, hepatic encephalopathy, or variceal bleeding, radiographic evidence of small ascites, or empiric use of lactulose/rifaximin for neurologic indications. The use of beta blockers was not exclusionary.
- History of suspected or confirmed hepatocellular carcinoma.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
GLE/PIB	AbbVie	Oral	Film-coated Tablet	100 mg/ 40 mg	16-001002 16-001003 16-005216

Duration of Treatment:

Subjects received GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Not applicable.

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 baseline polymorphisms at signature resistance-associated amino acid positions at baseline identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence were analyzed.

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

Pharmacokinetics:

Plasma concentrations for GLE and PIB were tabulated and summarized.

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 two primary efficacy analyses were evaluated using a fixed-sequence testing approach in the following order:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration was demonstrated if the lower bound of the 2-sided 95% CI for the percentage of subjects with HCV GT1, GT2, GT4, GT5, or GT6 infection in the 8-week treatment duration achieving SVR_{12} was greater than 94% in the per-protocol (PP) population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration was demonstrated if the lower bound of the 2-sided 95% CI for the percentage of subjects with HCV GT1, GT2, GT4, GT5, or GT6 infection in the 8-week treatment duration achieving SVR_{12} was greater than 93% in the intent-to-treat (ITT) population.

For both primary efficacy analyses, the percentage of subjects achieving SVR_{12} were summarized with a 2-sided 95% CI, calculated using the normal approximation to the binomial distribution. If the number of subjects who failed to achieve SVR_{12} rate was less than 5, the Wilson's score method was used to calculate the CI.

Statistical Methods (Continued)

The two key secondary efficacy analyses were to be performed only if success was demonstrated for both primary efficacy analyses, following a fixed-sequence testing procedure:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration was demonstrated if the lower bound of the 2-sided 95% CI for the percentage of subjects with HCV GT1, GT2, GT3, GT4, GT5, or GT6 infection in the 8-week treatment duration achieving SVR_{12} was greater than 94% in the per-protocol (PP) population.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration was demonstrated if the lower bound of the 2-sided 95% CI for the percentage of subjects with HCV GT1, GT2, GT3, GT4, GT5, or GT6 infection in the 8-week treatment duration achieving SVR_{12} was greater than 93% in the intent-to-treat (ITT) population.

The following secondary and additional efficacy endpoints were to be summarized:

- The percentage of HCV GT3-infected subjects in the PP population who achieved SVR_{12};
- The percentage of HCV GT3-infected subjects in the ITT population who achieved SVR_{12};
- The percentage of subjects with on-treatment virologic failure;
- The percentage of subjects with post-treatment relapse;
- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects who achieve sustained virologic response 4 weeks postdosing (HCV RNA < LLOQ 4 weeks after the last actual dose of study drug);
- The percentage of subjects who achieve sustained virologic response 24 weeks postdosing (HCV RNA < LLOQ 24 weeks after the last actual dose of study drug);
- The percentage of subjects who experience post-treatment relapse after achieving SVR_{12}.

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.

Subgroup:

The percentage of subjects with SVR_{12} were 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.

Statistical Methods (Continued)

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® 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 postbaseline visit were summarized descriptively. The number and percentage of subjects with postbaseline values meeting toxicity grades and meeting potential hepatotoxicity criteria were summarized. The number and percentage of subjects with postbaseline values during the Treatment Period meeting prespecified criteria for potentially clinically significant vital sign values were summarized.

Summary/Conclusions

Efficacy Results:

The two primary efficacy analyses were assessed through a fixed-sequence testing procedure:

1. The first primary efficacy analysis was achieved. In the PP population, SVR_{12} was achieved by 100% (274/274) of subjects with HCV GT1, GT2, GT4, GT5, or GT6 infection. Efficacy was demonstrated, as the lower bound of the 95% CI was above the threshold of 94%.
2. The second primary efficacy analysis was achieved. In the ITT population, SVR_{12} was achieved by 98.2% (275/280) of subjects with HCV GT1, GT2, GT4, GT5, or GT6 infection. Efficacy was demonstrated, as the lower bound of the 95% CI was above the threshold of 93%.

Summary/Conclusions (Continued)

Primary Efficacy Analyses for GT1, GT2, GT4-6-infected Subjects: Virologic Response at Post Treatment Week 12 (SVR_{12}) (PP and ITT Populations)

	PP Population	ITT Population
Assessment	**GLE/PIB (N = 274[a])**	**GLE/PIB (N = 280)**
SVR_{12}, n/N (%)	274/274 (100)	275/280 (98.2)
95% CI[b]	98.6, 100.0	96.7, 99.8
Threshold (%)	94	93
Nonresponse, n/N (%)	0/274	5/280 (1.8)
Reason for nonresponse, n/N (%)		
Virologic failure	0/274	0/280
On-treatment virologic failure	0/274	0/280
Relapse	0/271	0/274
Non-virologic failure	0/274	5/280 (1.8)
Premature study drug discontinuation	0/274	1/280 (0.4)
HCV reinfection	0/274	0/280
Missing SVR_{12} data	0/274	4/280 (1.4)
Other	0/274	0/280

CI = confidence interval; GLE = glecaprevir; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; PIB = pibrentasvir; PP = per-protocol; QD = once daily; SVR_{12} = sustained virologic response 12 weeks postdosing GLE/PIB 300 mg/120 mg QD for 8 weeks

a. Six GT1, GT2, GT4–6 subjects in the ITT population were excluded from the PP population: 5 subjects with SVR_{12} nonresponse for non-virologic reasons and 1 subject with treatment duration < 52 days who achieved SVR_{12}.

b. Calculated using the normal approximation to the binomial distribution, unless the number of nonresponses was less than 5, then the Wilson's score method was used for the CI instead.

The two key secondary efficacy analyses were assessed through a fixed-sequence testing procedure:

1. The first key secondary efficacy analysis was achieved. In the PP population, SVR_{12} was achieved by 99.7% (334/335) of subjects with HCV GT1 – GT6 infection. Efficacy was demonstrated, as the lower bound of the 95% CI was above the threshold of 94%.
2. The second key secondary efficacy analysis was achieved. In the ITT population, SVR_{12} was achieved by 97.7% (335/343) of subjects with HCV GT1 – GT6 infection. Efficacy was demonstrated, as the lower bound of the 95% CI was above the threshold of 93%.

Summary/Conclusions (Continued)

Key Secondary Efficacy Analyses for GT1 – GT6-infected Subjects: Virologic Response at Post Treatment Week 12 (SVR_{12}) (PP and ITT Populations)

	PP Population	ITT Population
Assessment	**GLE/PIB (N = 335[a])**	**GLE/PIB (N = 343)**
SVR_{12}, n/N (%)	334/335 (99.7)	335/343 (97.7)
95% CI[b]	98.3, 99.9	96.1, 99.3
Threshold (%)	94	93
Nonresponse, n/N (%)	1/335 (0.3)	1/343 (0.3)
Reason for nonresponse, n/N (%)		
Virologic failure	1/335 (0.3)	0/343
On-treatment virologic failure	0/335	0/343
Relapse	1/332 (0.3)	1/336[c] (0.3)
Non-virologic failure	0/335	7/343 (2.0)
Premature study drug discontinuation	0/335	1/343 (0.3)
HCV reinfection	0/335	0/343
Missing SVR_{12} data	0/335	6/343 (1.7)
Other	0/335	0/343

CI = confidence interval; GLE = glecaprevir; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; PIB = pibrentasvir; PP = per-protocol; QD = once daily; SVR_{12} = sustained virologic response 12 weeks postdosing

GLE/PIB 300 mg/120 mg QD for 8 weeks

a. Eight GT1 – GT6 subjects in the ITT population were excluded from the PP population: 7 subjects with SVR_{12} nonresponse for non-virologic reasons and 1 subject with treatment duration < 52 days who achieved SVR_{12}.
b. Calculated using the normal approximation to the binomial distribution, unless the number of nonresponses was less than 5, then the Wilson's score method was used for the CI instead.
c. Seven subjects were excluded from the analysis of relapse: 3 subjects infected with GT1a, 3 subjects infected with GT1b, and 1 subject infected with GT3a.

SVR_{12} was achieved by 98.4% (60/61) of GT3-infected subjects in the PP population and 95.2% (60/63) of GT3-infected subjects in the ITT population.

No subject experienced on-treatment virologic failure; one (GT3a-infected) subject experienced relapse at Post-Treatment Week 4 and therefore did not achieve SVR_{12}. Of those subjects who achieved SVR_{12}, none relapsed during the SVR_{24} window ($Relapse_{24}$).

Resistance Results:

Based on phylogenetic analysis of NS3/4A or NS5A sequences from 339 subjects, 2 GT1, 3 GT2, 1 GT3, 4 GT4, 1 GT5, and 4 GT6 subtypes were identified in the study, including 94 GT1a, 135 GT1b, 12 GT2a, 9 GT2b, 5 GT2c, 62 GT3a, 4 GT4a, 1 GT4c, 7 GT4d, 1 GT4r, 1 GT5a, 4 GT6a, 1 GT6e, 2 GT6h, and 1 GT6l-infected subjects.

Summary/Conclusions (Continued)

Resistance Results (Continued):

Baseline polymorphisms at the key subset of amino acid positions in NS3 (positions 155, 156, or 168) were not detected in GT2-, GT4-, or GT6-infected subjects, and were detected in 0.9% (2/227), 4.8% (3/62), and 100% (1/1) of the GT1-, GT3a-, and GT5a-infected subjects, respectively. Baseline NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were not detected in the GT5a-infected subject, and were detected in 28.5% (65/228), 84.6% (22/26), 22.6% (14/62), 76.9% (10/13), and 25.0% (2/8) of the GT1-, GT2-, GT3a-, GT4-, or GT6-infected subjects, respectively. Of note, among GT3a-infected subjects 7 had A30K (n = 3) or Y93H (n = 4) in NS5A at baseline, and all achieved SVR_{12}. The presence of baseline polymorphisms did not impact treatment outcome with any HCV genotype or subtype for GT1 – GT6-infected subjects in this study.

One GT3a-infected subject experienced virologic failure. This subject had no baseline polymorphisms in NS3 or NS5A. At the time of failure, the subject had no treatment-emergent substitutions in NS3 and had A30K + Y93H in NS5A. At Post-Treatment Week 12, A30K, L31F, and Y93H were detectable in NS5A.

Pharmacokinetic Results:

GLE and PIB concentrations following administration of GLE/PIB 300/120 mg QD to treatment-naïve adults with compensated cirrhosis were similar between subjects with chronic HCV GT3 infection and those with HCV GT1, GT2, GT4 – 6 infection. There was no substantial drug accumulation for either GLE or PIB during the Treatment Period.

Safety Results:

The majority of subjects who experienced treatment emergent adverse events (TEAEs) had events with a maximum severity of Grade 1, with the most common (≥ 5% of subjects) being fatigue, pruritus, headache, and nausea. No TEAEs met the 10% cutoff. Study-drug related TEAEs experienced by ≥ 5.0% of subjects were fatigue, pruritus, and headache. A small percentage of subjects in the safety population (3.2% [11/343]) experienced a TEAE of Grade ≥ 3 in severity, one of which was considered related to study drug. No trend in the type and frequency of Grade ≥ 3 TEAEs was observed.

Six subjects experienced treatment emergent SAEs, none of which were assessed as related to study drug or led to treatment discontinuation. No subjects had a TEAE leading to premature discontinuation of study drug. One subject experienced a Grade 3 SAE of hepatocellular carcinoma on Day 225 (Post-Treatment Day 169) that was considered not related to study drug by the investigator.

Four subjects had Grade 3 hematology or chemistry values that worsened compared with baseline during the Treatment Period. The hematology or chemistry values were isolated and were not clinically significant. No case of Grade 4 hematology or chemistry values was identified.

No clinically meaningful observations were noted for vital signs or 12-lead electrocardiogram assessments.

Summary/Conclusions (Continued)

Conclusions:

- An 8-week regimen of GLE/PIB 300 mg/120 mg QD in treatment-naïve HCV GT1-, GT2-, GT4-, GT5-, or GT6-infected adult subjects with compensated cirrhosis achieved high efficacy (SVR_{12} of 100% in the PP population and 98.2% in the ITT population) with no virologic failures. The lower 95% confidence bounds of the SVR_{12} rates exceeded the pre-defined efficacy thresholds based on historical SVR_{12} rates with 12-weeks of treatment with GLE/PIB.
- An 8-week regimen of GLE/PIB 300 mg/120 mg QD in treatment-naïve HCV GT1– GT6-infected adults subjects with compensated cirrhosis achieved high efficacy (SVR_{12} of 99.7% in the PP population and 97.7% in the ITT population) with 1 virologic failure, an GT3a-infected subject. The lower 95% confidence bounds of the SVR_{12} rates exceeded the pre-defined efficacy thresholds based on historical SVR_{12} rates with 12-weeks of treatment with GLE/PIB.
- Among GT3-infected subjects, SVR_{12} was achieved by 98.4% (60/61) in the PP population and 95.2% (60/63) in the ITT population.
- High SVR_{12} rates were achieved irrespective of any baseline viral or host factors, including baseline HCV RNA level, HCV genotype and subtype, injection drug use, concomitant use of proton pump inhibitors, stable use of opiate substitution therapy, and presence of baseline NS3 and/or NS5A polymorphisms.
- No subjects experienced post-treatment relapse after achieving SVR_{12}.
- GLE/PIB 300 mg/120 mg QD demonstrated a favorable safety profile and was well tolerated, with mostly mild TEAEs. There were no study drug-related treatment emergent SAEs, no discontinuations due to TEAEs, and few occurrences of significant laboratory abnormalities. One subject reported a non-treatment-emergent, non-related postbaseline SAE of HCC. No new safety concerns specific to this population were identified.
- The data support the efficacy and safety of an 8-week treatment duration of GLE/PIB in treatment-naïve HCV-infected adults with compensated cirrhosis, regardless of genotype.