

Methodology (Continued):

All subjects administered at least 1 dose of study drug were to be followed for 24 weeks post-treatment to monitor for safety, HCV RNA, and the emergence and/or persistence of viral substitutions.

The planned total duration of the study (excluding screening) was 32 to 40 weeks for all subjects.

Number of Subjects (Planned and Analyzed):

Planned: approximately 120 subjects

Analyzed: 101 subjects were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Diagnosis:

The study population consisted of HCV treatment-naïve or treatment-experienced (i.e, IFN or pegIFN with or without RBV, or SOF plus RBV with or without peg IFN) HCV GT1-6-infected adult male and female subjects without cirrhosis or with compensated cirrhosis, who had CKD Stage 3b, Stage 4, or Stage 5.

Main Inclusion Criteria:

- Male or female (of non childbearing potential or using allowed contraceptive methods) at last 18 years of age time of Screening.
- Estimated Glomerular Filtration Rate (eGFR) < 45 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease (MDRD) method at Screening according to the following formula: $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Serum Creatinine})^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$, or were dialysis-dependent. Subjects requiring dialysis had to have been receiving dialysis for at least 1 month prior to enrollment, and may have been on hemodialysis or peritoneal dialysis.
- Positive for anti-HCV antibody at Screening and plasma HCV RNA \geq 1000 IU/mL at Screening
- Cirrhotic Subjects 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.

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.
- Current hepatitis B virus (HBV) or human immunodeficiency virus (HIV) infection on screening tests, defined as:
 - o A positive hepatitis B surface antigen (HBsAg), or;
 - o HBV deoxyribonucleic acid (DNA) > LLOQ in subjects with isolated positive hepatitis B core antibody (HBcAb) (i.e., negative HBsAg and Anti-HBsAg), or;
 - o A positive anti-HIV antibody.

Diagnosis and Main Criteria for Inclusion (Continued):

- 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 prior or current empiric use of lactulose/rifaximin for neurologic indications. Prophylactic use of beta blockers was not exclusionary.
- Clinical history of acute renal failure in the 3 months prior to Screening.
- History of severe, life-threatening, or other significant sensitivity to any excipients of the study drugs.
- History of any suspected or confirmed HCC.

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	16-001003

Duration of Treatment:

Subjects received GLE/PIB 300 mg/120 mg QD for 8, 12, or 16 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.

The primary efficacy variable was SVR₁₂ defined as HCV RNA < LLOQ 12 weeks after the last actual dose of study drug.

The secondary efficacy variables were on-treatment virologic failure and post-treatment relapse.

Resistance:

For all subjects who received GLE/PIB and with available samples, baseline polymorphisms at signature resistance-associated amino acid positions identified by next generation sequencing (NGS) were analyzed and compared to the appropriate prototypic reference sequence.

The following resistance information was analyzed for subjects receiving GLE/PIB who did not achieve SVR₁₂ and who had a post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid substitutions in available post-baseline samples identified by NGS and comparison to the baseline sequences, 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 substitutions by NGS.

Pharmacokinetic:

Individual plasma concentrations for GLE and PIB were tabulated and summarized for each subject by visit and for all subjects combined.

Criteria for Evaluation (Continued)**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 the percentage of subjects who achieved SVR₁₂ based on the overall population across treatment durations, genotypes, and cirrhosis status. The number and percentage of subjects in the intention-to-treat (ITT) population achieving SVR₁₂ were summarized with a 2-sided 95% confidence interval (CI), calculated using Wilson's score method.

The secondary efficacy endpoints were:

- The percentage of subjects with HCV 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 \geq LLOQ at the end of treatment with at least 6 weeks of treatment).
- The percentage of subjects with post-treatment HCV virologic relapse (defined as confirmed HCV RNA \geq LLOQ between end of treatment and 12 weeks after the last dose of study drug [Relapse₁₂ among subjects who completed treatment as planned with HCV RNA $<$ LLOQ at the end of treatment; excluding subjects who have been shown to be reinfected]).

For the analysis of post-treatment HCV virologic relapse, completion of treatment was defined as any subject with study drug duration of 52 days, 77 days, and 103 days or greater for subjects allocated to treatment durations of 8 weeks, 12 weeks, and 16 weeks, respectively.

For on-treatment virologic failure and post-treatment relapse, the number and percentage of subjects was summarized along with a 2-sided 95% CI using Wilson's score method.

Subgroup Analyses:

The percentage of subjects with SVR₁₂ in the ITT population was calculated with the corresponding 2 sided 95% Wilson score CIs for subgroup variables such as HCV GT subtype, prior HCV treatment history, dialysis type, and CKD stage at Screening.

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 sequence from baseline samples in order to accurately determine subtype.

Statistical Methods (Continued)

Pharmacokinetic:

Individual plasma concentrations for GLE and PIB were tabulated and summarized for each subject by visit 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 postbaseline values meeting toxicity grades and meeting potential hepatotoxicity criteria during treatment 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.

For cirrhotic subjects, a cross-tabulation of Child-Pugh score at baseline and specified post-baseline visits was generated. For subjects with CKD Stage 3b or 4 at Screening, a cross-tabulation of CKD stage at baseline and specified post-baseline visits; a summary of eGFR at Screening, end of treatment, and Post-treatment Week 4; and a summary of CKD stage change between Screening and end of treatment were generated.

Summary/Conclusions

Efficacy Results:

The study population was comprised of 101 subjects infected with HCV (52 subjects GT1 [52.5%], 27 subjects GT2 [27.3%], 15 subjects GT 3 [15.2%], 4 subjects GT 4 [4.0%], 1 subject mixed genotype [1.0%], and 2 subjects GT missing).

Sustained virologic response 12 weeks postdosing was achieved by 97.0% (98/101; 95% CI: 91.6%, 99.0%) of subjects in the ITT population.

No subjects relapsed after achieving SVR₁₂. Results for sustained virologic response 24 weeks postdosing (SVR₂₄) (98.0%, 95% CI: 93.1%, 99.5%) were consistent with the primary efficacy results (SVR₁₂). The agreement between SVR₁₂ and SVR₂₄ was 99.0%.

Resistance Results:

Based on phylogenetic analysis of NS3/4A or NS5A sequences from 99 subjects, 3 GT1, 5 GT2, 1 GT3, and 2 GT4 subtypes were identified in the study, including 20 GT1a (20.2%), 33 GT1b (33.3%), 1 GT1g (1.0%), 9 GT2a (9.1%), 6 GT2b (6.1%), 9 GT2c (9.1%), 2 GT2j (2.0%), 1 GT2k (1.0%), 14 GT3a (14.1%), 3 GT4a (3.0%), and 1 GT4d (1.0%).

Baseline polymorphisms at the key subset of amino acid positions in NS3 (positions 155, 156, or 168) were not detected in any of the GT1-4-infected subjects. NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 46.3% (37/80) of the GT1-4-infected subjects. The presence of baseline polymorphisms had no impact on treatment outcome in subjects infected with any HCV subtype in this study, as none of the subjects experienced virologic failure.

Summary/Conclusions (Continued)

Pharmacokinetic Results:

Pharmacokinetic exposures of GLE and PIB in adults with chronic HCV GT1-6 infection with CKD Stage 3b, Stage 4, and Stage 5, regardless of cirrhosis status or prior treatment experience were summarized. GLE and PIB concentrations quickly increased postdose to the maximum level by approximately 4 hours. There was no substantial drug accumulation for either GLE or PIB during the Treatment Period.

Safety Results:

The majority (56.4%) 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), with the most common AEs ($\geq 5.0\%$ of subjects) being pruritus (15.8%), bronchitis (5.9%), hypertension (5.9%), and pruritus generalized (5.9%). There were no deaths during the study. Twelve subjects experienced treatment-emergent SAEs, none of which were considered related to study drug by the investigator. Two subjects had nonserious AEs leading to premature discontinuation of study drug 1 of which (pruritus) was considered related to study drug by the investigator. No subject experienced an event of hepatic decompensation, and there were no suspected cases of drug-induced liver injury. No clinically important trends in vital signs were observed, and no clinically significant postbaseline abnormal ECG findings were observed. The majority of subjects with CKD Stage 3b or 4 at Screening experienced no changes in CKD stage between screening and end-of-treatment. No evidence of an increased risk of renal events and of progression of renal disease among subjects with CKD Stage 3b was observed.

Conclusions:

- In subjects with CKD Stages 3b and 4 and CKD Stage 5, including subjects receiving dialysis, the fixed-dose combination of GLE/PIB 300 mg/120 mg QD given for 8, 12, or 16 weeks demonstrated high efficacy; the SVR₁₂ rate was 97.0% (95% CI: 91.6%, 99.0%).
- Pharmacokinetic exposures of GLE and PIB in adults with chronic HCV GT1-6 infection with CKD Stage 3b, Stage 4, and Stage 5, regardless of cirrhosis status or prior treatment experience were summarized. GLE and PIB concentrations quickly increased postdose to the maximum level by approximately 4 hours. There was no substantial drug accumulation for either GLE or PIB during the Treatment Period.
- No subjects experienced virologic failure.
- High efficacy was observed regardless of baseline host or viral factors, including demographics, baseline HCV RNA levels, HCV genotype, CKD stage, cirrhosis status, relevant comorbidities, prior treatment history, or presence of baseline polymorphisms in NS3 and/or NS5A.
- Results for SVR₂₄ (98.0%, 95% CI: 93.1%, 99.5%) were consistent with the primary efficacy results with 99.0% agreement between SVR₁₂ and SVR₂₄. No subjects relapsed after achieving SVR₁₂.
- The fixed-dose combination of GLE/PIB 300 mg/120 mg QD administered for 8, 12, or 16 weeks was well-tolerated and demonstrated a favorable safety profile in subjects with CKD Stage 3b, 4, or 5. No new safety findings were identified.