

1.0**Title Page****Statistical Analysis Plan****Study M16-127**

**A Multicenter, Open-Label Study to Evaluate the
Efficacy and Safety of Glecaprevir/Pibrentasvir in
Renally-Impaired Adults with Chronic Hepatitis C
Virus Genotype 1 – 6 Infection (EXPEDITION-5)**

Date: 06 Feb 2018

Version 1.0

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|-------------|---|-----------|
| 2.0 | Table of Contents | |
| 1.0 | Title Page | 1 |
| 2.0 | Table of Contents | 2 |
| 3.0 | Introduction..... | 5 |
| 4.0 | Study Objectives, Design and Procedures..... | 5 |
| 4.1 | Objectives | 5 |
| 4.2 | Design Diagram | 6 |
| 4.3 | Sample Size..... | 7 |
| 4.4 | Planned Analyses | 8 |
| 5.0 | Analysis Populations | 8 |
| 5.1 | Definitions of Analysis Populations..... | 8 |
| 5.1.1 | Intention-to-Treat (ITT) Population | 8 |
| 5.1.2 | Modified Intention-to-Treat (mITT) Populations | 9 |
| 5.1.3 | Safety Population | 9 |
| 6.0 | Analysis Conventions | 9 |
| 6.1 | Definition of Baseline, Final Treatment, and Final Post-Treatment Assessments | 9 |
| 6.1.1 | Baseline..... | 9 |
| 6.1.2 | Study Days | 10 |
| 6.2 | Definition of Analysis Windows..... | 10 |
| 6.3 | Missing Data Imputation | 13 |
| 7.0 | Demographics, Baseline Characteristics, Medical History, and Other Medications | 14 |
| 7.1 | Demographic and Baseline Characteristics | 14 |
| 7.2 | Medical History..... | 20 |
| 7.3 | Prior, Concomitant and Post-Treatment Medications | 21 |
| 8.0 | Subject Disposition..... | 21 |
| 8.1 | Disposition of Safety Population | 21 |
| 9.0 | Study Drug Exposure and Compliance..... | 22 |
| 9.1 | Exposure | 22 |
| 9.2 | Compliance | 23 |
| 10.0 | Efficacy Analysis | 23 |

| | | |
|-------------|--|-----------|
| 10.1 | General Considerations..... | 23 |
| 10.2 | Handling of Multiplicity | 28 |
| 10.3 | Primary Efficacy Analysis | 28 |
| 10.4 | Secondary Efficacy Analyses | 28 |
| 10.5 | Sensitivity Analyses for SVR | 29 |
| 10.5.1 | Imputation Approaches..... | 29 |
| 10.6 | Efficacy Subgroup Analysis | 29 |
| 10.7 | Additional Efficacy Analyses | 30 |
| 10.8 | Resistance Analyses | 31 |
| 10.8.1 | Presence of Baseline Polymorphisms for Subgroup Analyses of SVR ₁₂ | 36 |
| 10.9 | Patient Reported Outcomes | 37 |
| 11.0 | Safety Analysis..... | 38 |
| 11.1 | General Considerations..... | 38 |
| 11.2 | Analysis of Adverse Events..... | 38 |
| 11.2.1 | Treatment-Emergent Adverse Events..... | 38 |
| 11.2.2 | Tabulations of Treatment-Emergent Adverse Events | 38 |
| 11.2.3 | Adverse Events of Special Interest..... | 41 |
| 11.2.4 | Listings of Adverse Events | 42 |
| 11.3 | Analysis of Laboratory Data..... | 42 |
| 11.3.1 | Variables and Criteria Defining Abnormality..... | 42 |
| 11.3.2 | Statistical Methods | 44 |
| 11.4 | Analysis of Vital Signs and Weight | 48 |
| 11.4.1 | Variables and Criteria Defining Abnormality..... | 48 |
| 11.4.2 | Statistical Methods | 48 |
| 11.5 | Analysis of Child-Pugh Score..... | 49 |
| 12.0 | Summary of Changes | 49 |
| 12.1 | Summary of Changes Between the Latest Version of the Protocol and SAP | 49 |
| 13.0 | References..... | 49 |

List of Tables

| | | |
|-----------|---|----|
| Table 1. | Analysis Time Windows for HCV RNA and Resistance Endpoints, Safety Laboratory and Vital Sign Measurements, Child Pugh Scores and PRO Instruments (Treatment Period) | 11 |
| Table 2. | Analysis Time Windows for HCV RNA and Resistance Endpoints (Post-Treatment Period) | 12 |
| Table 3. | Analysis Time Windows for Safety Laboratory and Vital Sign Measurements, Child Pugh Scores and PRO Instruments (Post-Treatment Period) | 12 |
| Table 4. | Definition of Chronic Kidney Disease Stages | 16 |
| Table 5. | Baseline Fibrosis Stage..... | 17 |
| Table 6. | Child-Pugh Classification of Severity of Cirrhosis..... | 19 |
| Table 7. | Medical/Surgical History eCRF | 20 |
| Table 8. | Signature Amino Acid Positions and the Key Subset of Amino Acid Positions | 32 |
| Table 9. | Amino Acid Positions for Subgroup Analysis | 36 |
| Table 10. | Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values | 44 |
| Table 11. | Criteria for Potentially Clinically Significant Vital Sign Values | 48 |

List of Figures

| | | |
|-----------|-----------------------|---|
| Figure 1. | Study Schematic | 7 |
|-----------|-----------------------|---|

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the AbbVie Statistics and Statistical Programming Departments for Study M16-127. Study M16-127 evaluates the efficacy and safety of GLE/PIB in adults with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection with compensated cirrhosis or without cirrhosis and with chronic renal impairment in both HCV treatment-naïve (TN) and interferon/pegylated interferon (IFN), ribavirin (RBV) and/or SOF treatment-experienced (TE) subjects.

This SAP (Version 1.0) provides details to further elaborate the statistical methods outlined in Clinical Study Protocol M16-127 incorporating Administrative Change 1 and 2 and Amendment 1 and 2 and 3 dated 30 January 2018, and describes analysis conventions to guide the statistical programming. Analyses will be performed using SAS[®] Version 9.4 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objectives of this study are to assess the efficacy (by evaluating the percentage of subjects achieving SVR₁₂) and safety of GLE/PIB in adults with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection with compensated cirrhosis or without cirrhosis and with chronic renal impairment in both HCV TN and TE subjects. The efficacy of GLE/PIB will be assessed based on the overall population (i.e., across treatment durations, genotypes, and cirrhosis status), and the safety of GLE/PIB will be assessed by treatment duration and cirrhosis status across genotypes.

The secondary objectives are to assess the efficacy of GLE/PIB based on the overall population (i.e., across treatment durations, genotypes, and cirrhosis status) by evaluating the following:

- The percentage of subjects with HCV on-treatment virologic failure;
- The percentage of subjects with HCV virologic relapse.

4.2 Design Diagram

This is a Phase 3b, open-label, non-randomized, multicenter study to evaluate the efficacy and safety of GLE/PIB for 8, 12, or 16 weeks in HCV GT1 – 6-infected subjects with chronic renal impairment, with compensated cirrhosis or without cirrhosis, who are either HCV TN or prior TE with interferon [IFN] or pegylated IFN [pegIFN] with or without RBV, or sofosbuvir [SOF] plus RBV with or without pegIFN. This study will consist of a Screening Period, a Treatment Period, and a Post-Treatment Period. A study schematic is shown below in [Figure 1](#).

The study is designed to enroll approximately 120 eligible subjects. The study enrollment will be monitored to meet the following non-mutually exclusive enrollment criteria:

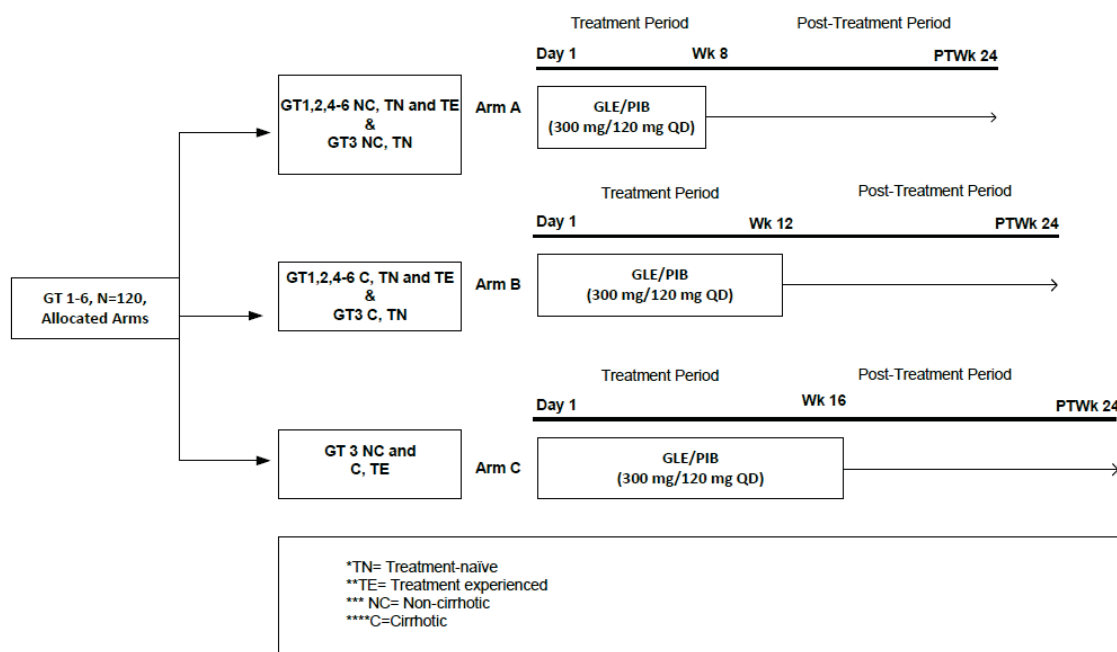
(1) up to approximately 40 subjects with Stage 3b CKD, (2) up to approximately 75 HCV GT1-infected subjects, (3) up to approximately 30 subjects with compensated cirrhosis.

Subjects will be enrolled into one of the following treatment arms:

- Arm A: HCV GT1, 2, 4 – 6 subjects without cirrhosis who are TN or TE and HCV GT 3 subjects without cirrhosis who are TN will be treated for 8 weeks.
- Arm B: HCV GT1, 2, 4 – 6 subjects with compensated cirrhosis who are TN or TE and HCV GT 3 subjects with compensated cirrhosis who are TN will be treated for 12 weeks.
- Arm C: All HCV GT3 subjects who are TE will be treated for 16 weeks.

Subjects with mixed HCV genotype infection should receive whichever duration is longer based on their genotypes, cirrhosis status, and treatment experience. For subjects with an indeterminate genotype, treatment duration will default to the respective GT3 duration based upon treatment-experience and cirrhosis status.

Figure 1. Study Schematic



4.3 Sample Size

It is anticipated that approximately 120 HCV GT1 – 6 infected subjects with chronic renal impairment, with compensated cirrhosis or without cirrhosis, who are either HCV TN or TE with IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN will be enrolled in the study. No formal hypothesis is being tested. If the observed SVR_{12} rate in this study is 97% among 120 HCV GT1 – 6 renally impaired subjects, then the half-width of the 2-sided 95% confidence interval (CI) using the normal approximation to the binomial distribution is 0.031 (nQuery Advisor, Version 8.0, Statistical Solutions, Ltd., Boston, MA).

4.4 Planned Analyses

All analyses will be conducted by statisticians and programmers at AbbVie or designees according to the methodologies specified in this SAP.

The primary analysis will occur after all subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinued from the study. For the primary analysis, data will be locked after performing appropriate data cleaning.

The end-of-study analysis will be conducted when all subjects enrolled in the study have completed the Post-Treatment Week 24 Visit or prematurely discontinued from the study. Data collected after the primary analysis will be added to a new version of the database which will be cleaned and locked at the end of the study. Results from the final analysis will be described in the clinical study report (CSR).

There is no intention of stopping the study early based on efficacy findings the primary analysis. The intention is to follow all subjects who receive study drug for 24 weeks following treatment.

5.0 Analysis Populations

5.1 Definitions of Analysis Populations

5.1.1 Intention-to-Treat (ITT) Population

All subjects who receive at least one dose of study drug will be included in the ITT population. Demographic, baseline characteristic, exposure, concomitant medication and medical history analyses will be performed on the ITT population overall and according to the treatment assignment, i.e., subject grouping will be based on the arm to which the subject was assigned. Efficacy analyses will be performed on the overall ITT population, combining Arms A, B and C which are the recommended duration per labelling.

5.1.2 Modified Intention-to-Treat (mITT) Populations

Sensitivity analyses of SVR₁₂ as described in Section 10.5 will be performed on the ITT population modified to exclude subjects who did not achieve SVR₁₂ for reasons other than virologic failure (mITT-VF).

5.1.3 Safety Population

All subjects who receive at least one dose of study drug will be included in the safety population. Safety analysis will be performed on the overall ITT population, combining Arms A, B and C.

6.0 Analysis Conventions

6.1 Definition of Baseline, Final Treatment, and Final Post-Treatment Assessments

6.1.1 Baseline

The baseline value refers to the last non-missing measurement collected before the first dose of study drug is received. The protocol specifies that all Day 1 assessments are to be performed prior to administering the first dose of study drug. Therefore, all Day 1 assessments for which time is not collected will be assumed to be pre-dose and the baseline value will be the last non-missing measurement collected on or before the first day of study drug administration.

All Day 1 assessments with time available must be before the time of first dose to be considered baseline, and the last non-missing measurement collected before the date and time of the first dose of study drug will be considered the baseline value. If multiple measurements that are prior to dosing are recorded on the same date and with the same time or if time is not available, then the average of these measurements will be considered as the baseline value. The same baseline value will be used for analyses of the Treatment and Post-Treatment Periods.

Safety assessments that are related to a serious adverse event that occurred on the first dose day are excluded when applying this algorithm.

6.1.2 Study Days

Study Days (Days Relative to the First Dose of Study Drug)

Study days are calculated for each time point relative to the first dose of study drug. Study days are negative values when the time point of interest is prior to the first study drug dose day. Study days are positive values when the time point of interest is after the first study drug dose day. There is no Study Day 0. Study Day 1 is the day of the first dose of study drug.

Study Drug End Days (Days Relative to the Last Dose of Study Drug)

Study drug end days are calculated for each time point relative to the last dose of study drug. The last day of study drug dosing is defined as Study Drug End Day 0. Days before it have negative study drug end days and days after it have positive study drug end days.

Final Treatment Value

The final treatment value is defined as the last non-missing measurement collected after Study Day 1 and on or before Study Drug End Day 2.

Final Post-Treatment Value

The final post-treatment value for each subject is the last non-missing measurement collected after Study Drug End Day 2 and on or before Study Drug End Day 999.

6.2 Definition of Analysis Windows

For efficacy analyses of HCV RNA, the time windows specified in [Table 1](#) and [Table 2](#) describe how efficacy data are assigned to protocol-specified time points during the Treatment and Post-Treatment Periods, respectively. All time points and corresponding time windows are defined based on the date/time of blood sample collection.

For safety laboratory data, PRO data, Child Pugh score and vital sign data, the time windows specified in [Table 1](#) and [Table 3](#) describe how data are assigned to protocol-specified time points.

If more than one assessment is included in a time window, the assessment closest (except in analyses of SVR) to the nominal time will be used. If there are two observations equally distant to the nominal time, the latest one will be used in analyses. For analyses of SVR (e.g., SVR₁₂), the last value in the window will be used.

If multiple measurements are made on the same day for a safety laboratory parameter or a vital sign parameter, the average of the values will be used to calculate descriptive statistics and in analyses of the mean change from baseline. For summaries of shifts from baseline and potentially clinically significant values, multiple values on the same day will not be averaged; all values will be considered for these analyses.

Table 1. Analysis Time Windows for HCV RNA and Resistance Endpoints, Safety Laboratory and Vital Sign Measurements, Child Pugh Scores and PRO Instruments (Treatment Period)

| Scheduled Visit | Nominal Day (Study Day) | Time Window (Study Day Range) |
|------------------------------------|---|----------------------------------|
| Day 1/Baseline ^a | 1 | ≤ 1 ^a |
| Week 4 | 28 | 2 to 42 |
| Week 8 | 56 | 43 to 70 |
| Week 12 ^{b,c} | 84 | 71 to 98 |
| Week 16 ^c | 112 | 99 to 126 |
| Final Treatment Visit ^d | 2 to ≤ 2 days after last dose of study drug | |

a. Day of first dose of study drug.

b. For 12-week and 16-week treatment duration only.

c. For 16-week treatment duration only.

d. The last value within the window will be used to define the Final Treatment Visit value. The upper bound of this Final window is Study Drug End Day 2. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Note: For all windows, data must be on or before Study Drug End Day 2. The result closest to the scheduled time point will be used. PRO instruments are collected at Day 1, Week 4, Week 12 (Arm C only) and End of Treatment Visit, which can be at Week 8, 12 or 16 depending on treatment assignment, or Premature Discontinuation Visit.

Table 2. Analysis Time Windows for HCV RNA and Resistance Endpoints (Post-Treatment Period)

| Scheduled Visit^a | Nominal Day (Study Drug End Day) | Time Window (Study Drug End Day Range) |
|------------------------------------|---|---|
| Post-Treatment Week 4 | 28 | 3 to 56 |
| Post-Treatment Week 12 | 84 | 57 to 126 |
| Post-Treatment Week 24 | 168 | 127 to 999 |
| SVR ₄ ^b | 28 | 3 to 56 |
| SVR ₁₂ ^b | 84 | 57 to 126 |
| SVR ₂₄ ^b | 168 | 127 to 210 |

a. Post-Treatment Visits are applicable for subjects who received at least one dose of study drug.

b. For SVR windows, the last value in the window will be used.

Note: The result closest to the scheduled time point will be used, except for SVR₄, SVR₁₂, and SVR₂₄. For all windows, data must occur after Study Drug End Day 2. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Table 3. Analysis Time Windows for Safety Laboratory and Vital Sign Measurements, Child Pugh Scores and PRO Instruments (Post-Treatment Period)

| Scheduled Visit^a | Nominal Day (Study Drug End Day) | Time Window (Study Drug End Day Range) |
|---|---|---|
| Post-Treatment Week 4 | 28 | 3 to 56 |
| Post-Treatment Week 12 | 84 | 57 to 126 |
| Post-Treatment Week 24 | 168 | 127 to 999 |
| Final Post-Treatment Visit ^b | > 2 days after last dose of study drug | |

a. Post-Treatment Visits are applicable for subjects who received at least one dose of study drug.

b. The last value within the Post-Treatment Period window will be used to define the Final Post-Treatment visit value. The lower bound of this Final window is Study Drug End Day 3. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Note: The result closest to the scheduled time point will be used. For all windows, data must occur after Study Drug End Day 2. Vital signs are collected at every post-treatment visit; hematology, chemistry and coagulation panels are collected at PTW4 or PT D/C (if subject discontinued prior to PTW4). PRO instruments and Child Pugh Scores are collected at PTW12 and PTW24 (or PT D/C).

6.3 Missing Data Imputation

Missing Data Imputation for SVR

HCV RNA values will be selected for analysis based on the analysis windows defined in Section 6.2.

For analyses of SVR, subjects missing visit values will have backward imputation applied, if possible. For backward imputation, if the nearest HCV RNA value after the SVR window is unquantifiable or undetectable, then it will be used to impute the HCV RNA value in the SVR window. If a subject is missing an HCV RNA value within the appropriate SVR window after performing backward imputation, then this value will be imputed with an HCV RNA value from a local laboratory if present; otherwise, the HCV RNA value will be missing. Subjects with missing HCV RNA data in the analysis window, after imputations, will be imputed as a failure.

Regardless of the imputation method described above, if a subject starts another treatment for HCV, then all HCV RNA values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses. The subject will be considered a failure for summaries of viral response at all time points after the start of the new HCV treatment.

Missing Data Imputation for Virologic Failure

If HCV RNA values from the central laboratory are missing but a local laboratory value is present in the appropriate time period, then the local laboratory value will be used to assess post-treatment relapse and on-treatment virologic failure.

Missing Data Imputation for PRO Questionnaires

If a respondent answers at least 50% of the items in a multi-item scale of the Kidney Disease Quality of Life (KDQOL-36), the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing.

If a subject starts another treatment for HCV, then all PRO assessment values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses.

7.0 Demographics, Baseline Characteristics, Medical History, and Other Medications

The ITT population will be used to summarize demographics, baseline characteristics, medical history and previous, concomitant, and post-treatment medications; data will be summarized across all subjects and by assigned treatment arm.

7.1 Demographic and Baseline Characteristics

Categorical demographic and baseline characteristic variables will be summarized with the number and percentage of subjects in each category. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, maximum and minimum). For categorical variables, the number of missing observations will be displayed, if applicable, on the summary tables. Percentages will be calculated based on the number of non-missing observations.

Continuous demographic and baseline characteristics include age, weight, height, body mass index (BMI), baseline \log_{10} HCV RNA level, creatinine clearance (Cockcroft-Gault calculation), eGFR (using the modification of diet in renal disease [MDRD] formula), platelet count, albumin, GGT, APRI, FIB-4, AST, ALT, and total, direct and indirect bilirubin.

Categorical demographic and baseline characteristics include:

- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Sex (male or female);
- Race and black race: black or non-black;
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Geographic region (North America, Europe, or rest of world);

- Country;
- Baseline BMI (< 30 or ≥ 30 kg/m²);
- HCV genotype and subtype (using central laboratory results and final genotype/subtype results, see Section 10.8);
- Prior HCV treatment history (naïve or experienced);
- For treatment-experienced subjects, type of previous regimen (IFN- or SOF-based);
- Baseline cirrhosis status (yes/no);
- For cirrhotic subjects, Baseline Child-Pugh score (5, 6, or > 6);
- Chronic Kidney Disease stage at screening (Stage 3b, Stage 4, Stage 5 without dialysis, or Stage 5 requiring dialysis);
- For treatment-experienced subjects, type of non-response to previous treatment (on-treatment non-responder, breakthrough, post-treatment relapse, or unknown/other);
- Baseline HCV RNA level ($< 1,000,000$; $\geq 1,000,000$ to $< 2,000,000$; or $\geq 2,000,000$ IU/mL);
- Baseline platelet count (< 90 or $\geq 90 \times 10^9$ /L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline eGFR (< 15 , ≥ 15 to < 30 , ≥ 30 to < 45 , or ≥ 45 mL/min/1.73 m²);
- Baseline creatinine clearance (< 15 , or ≥ 15 mL/min);
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, or F4);
- Concomitant use of Proton Pump Inhibitors (PPIs);
- Concomitant use of Statins (yes/no);
- Dialysis at screening (yes/no);
- For dialysis subjects, type of dialysis (hemodialysis, peritoneal dialysis, or other);
- Tobacco use (user, ex-user, or non-user);
- Alcohol use (drinker, ex-drinker, or non-drinker);
- Injection drug use (yes, within last 12 months; yes, more than 12 months ago; or no);

- Use of stable opiate substitution (yes/no);
- History of diabetes (yes/no);
- History of depression or bipolar disorder (yes/no);
- History of bleeding disorders (yes/no);
- History of cardiovascular disease (yes/no);
- History of hypertension (yes/no);

Summaries of baseline resistance are described in Section 10.8.

For TE subjects, any regimen that contains SOF with or without IFN or RBV is SOF-based. Otherwise, any regimen that contains IFN with or without RBV is IFN-based.

Any concomitant medication coded to the WHO Drug Dictionary ATC code of A02BC will be counted as a PPI. Any concomitant medication coded to the WHO Drug Dictionary ATC code of C10AA or C10BX will be counted as a statin.

CKD categorization at screening is defined according to eGFR and requirement of dialysis in Table 4 below:

Table 4. Definition of Chronic Kidney Disease Stages

| CKD Stage | eGFR (mL/min/1.73 m ²)* |
|-----------|-------------------------------------|
| 3b | 30 to < 45 |
| 4 | 15 to < 30 |
| 5 | < 15 or requiring dialysis |

* $\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Serum Creatinine})^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}).$

Dialysis at screening is defined as any dialysis that started prior to the Day 1 visit based on the eCRF "Dialysis Treatment Prior to and Initiated During Study." For subjects requiring dialysis, hemodialysis is defined as intermittent hemodiafiltration, intermittent hemodialysis, intermittent hemofiltration, continuous RRT, or sustained low efficiency (daily) dialysis; peritoneal dialysis is defined as automated peritoneal dialysis or continuous ambulatory peritoneal dialysis.

Baseline fibrosis stage is defined for subjects with non-missing liver biopsy scores, FibroScan scores, or FibroTest scores. Only one score will be used to categorize each subject even if a subject has more than one score recorded. If a biopsy score is present, then it will be used to categorize the subject, regardless of the FibroScan/FibroTest score. Similarly, if a FibroScan score is present along with a FibroTest score, then the FibroScan score will be used to categorize the subject. If biopsy and FibroScan scores are not present and more than one FibroTest result is available, then the baseline FibroTest result (i.e., last non-missing FibroTest result on or before Day 1) will be used to categorize the subject. Subjects will be categorized as F0 – F1, F2, F3 or F4 according to [Table 5](#).

Table 5. Baseline Fibrosis Stage

| Baseline Fibrosis Stage, Metavir Equivalents | Liver Biopsy Metavir, Batts Ludwig, Knodell, IASL, Scheuer, or Laennec Score | Liver Biopsy Ishak Score | FibroScan (kPa) | FibroTest [*] |
|--|--|--------------------------|-----------------|------------------------|
| F0 – F1 | 0 or 1 | 0, 1, or 2 | < 8.8 | ≤ 0.48 |
| F2 | 2 | 3 | ≥ 8.8 to < 9.6 | 0.49 to 0.58 |
| F3 | 3 | 4 | ≥ 9.6 to < 12.5 | 0.59 to 0.74 |
| F4 | 4 | ≥ 5 | ≥ 12.5 | ≥ 0.75 |

* APRI will not be used to derive baseline Fibrosis Stage. However, per inclusion/exclusion criteria, subjects need to have concordant FibroTest and APRI scores in order to determine eligibility.

The central laboratory calculates the estimated creatinine clearance (CrCl) based on the following Cockcroft-Gault formula:

$$\text{CrCl (mL/min)} = [(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})] / [\text{serum creatinine (mg/dL)} \times 72].$$

The central laboratory calculates the eGFR by MDRD based on the following formula:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Serum Creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}).$$

Baseline APRI and FIB-4 are calculated by the equations below. Subjects who do not have concurrent AST and platelet values at baseline will be excluded from the summary of baseline APRI. Age is defined in years at baseline. Subjects who do not have concurrent values of AST, ALT and platelet count at baseline or subjects who are missing age will be excluded from the summary of FIB-4.

$$\text{APRI} = \frac{\frac{\text{AST Level (U/L)}}{\text{AST (Upper Limit of Normal)(U/L)}}}{\text{Platelet Count (10}^9\text{/L)}} \times 100$$

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}}$$

Presence or absence of cirrhosis will be determined as collected in IRT/EDC ("subject's cirrhosis status?" – "Compensated cirrhotic" or "Non-cirrhotic").

Baseline Child-Pugh score is determined by the Day 1 assessment of ascites and hepatic encephalopathy along with the baseline values of total bilirubin, serum albumin, and international normalized ratio (INR). The Child-Pugh score is the sum of the points assigned for each of the five observed findings as defined in [Table 6](#).

Table 6. Child-Pugh Classification of Severity of Cirrhosis

| Parameter | Points Assigned for Observed Findings | | |
|--|---------------------------------------|---|---|
| | 1 | 2 | 3 |
| Total bilirubin, $\mu\text{mol/L}$ (mg/dL) | < 34.2 (< 2) | 34.2 – 51.3 (2 – 3) | > 51.3 (> 3) |
| Serum albumin, g/L (g/dL) | > 35 (> 3.5) | 28 – 35 (2.8 – 3.5) | < 28 (< 2.8) |
| INR | < 1.7 | 1.7 – 2.3 | > 2.3 |
| Ascites* | None | Slight | Moderate to severe |
| Hepatic encephalopathy** | None | Grade 1 or 2 (or suppressed with medication) | Grade 3 or 4 (or refractory to medication) |

Child-Pugh category A: 5 – 6 points; Child-Pugh category B: 7 – 9 points; Child-Pugh category C: 10 – 15 points

* None;

Slight ascites = Ascites detectable only by ultrasound examination;

Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen;

Severe ascites = Large or gross ascites with marked abdominal distension.

** None: normal consciousness, personality, neurological examination, electroencephalogram;

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves;

Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves;

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves;

Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

Histories of diabetes, bleeding disorders, depression or bipolar disorder, hypertension, and cardiovascular disease will be based on the Medical/Surgical History eCRF, as defined in Table 7.

Table 7. Medical/Surgical History eCRF

| Medical/Surgical History eCRF | | |
|--------------------------------|-----------------------------------|---|
| Subgroup | Body System | Condition/Diagnosis |
| Diabetes | Metabolic | Diabetes mellitus |
| Bleeding disorders | Blood | Clotting/bleeding problems Factor deficiency Hemophilia Von Willebrand disease |
| Depression or bipolar disorder | Neurologic and Psychiatric System | Bipolar disorder Depression |
| Cardiovascular disease | Cardiovascular | Angina Cardiac arrhythmia Cardiovascular disease Congenital heart disease Congestive heart failure Coronary artery disease Hypertension Myocardial infarction Myocarditis Peripheral vascular disease-arterial Peripheral vascular disease-venous Valvular heart disease Vasculitis |
| Hypertension | Cardiovascular | Hypertension |

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Prior, Concomitant and Post-Treatment Medications

A prior medication is defined as any medication taken prior to the date of the first dose of study drug (GLE/PIB). A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken on or after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug. A post-treatment medication for the treatment of HCV is defined as any medication taken on or after the last dose of study drug and entered as "Post-treatment HCV medications" on the eCRF.

The number and percentage of subjects taking prior medications, concomitant medications, and post-treatment HCV medications will be summarized by generic drug name based on the WHO Drug Dictionary. The prior HCV medications taken by treatment experienced subjects and collected on the "Last Prior HCV Therapy" and "Second to Last Prior HCV Therapy" eCRFs will be summarized separately from other prior medications, and will not be included in the summary of all prior and concomitant medication.

8.0 Subject Disposition

The number and percentage of subjects who screen failed for any reason will be summarized for subjects who screen failed and by each screen fail reason.

8.1 Disposition of Safety Population

The number of subjects in each of the following categories will be summarized by investigator for each treatment arm and overall.

- Enrolled subjects;
- Subjects who took at least one dose of study drug;
- Subjects who completed study drug;
- Subjects who prematurely discontinued study drug;

- Subjects who completed the study;
- Subjects who prematurely discontinued from the study;
- Subjects ongoing in the Post-Treatment Period (if applicable at the time of analysis).

The number and percentage of subjects who discontinued study drug will be summarized by reason (all reasons) and by primary reason (per eCRF) for each treatment arm and overall. Similar summaries will be provided for discontinuations from the study.

The number and percentage of subjects with reported study drug interruptions will be summarized by treatment arm. Reasons for study drug interruptions will be presented in the CSR listings.

9.0 Study Drug Exposure and Compliance

Exposure and compliance will be summarized on the ITT population by treatment arm and overall.

9.1 Exposure

The duration of exposure to study drug will be summarized for each treatment arm and overall in the safety population. Duration of exposure is defined for each subject as the last study drug dose date minus the first study drug dose date plus 1 day.

During each treatment period, descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for exposure. Study drug duration will also be summarized with frequencies and percentages using the following categories:

- 1 to 15 days
- 16 to 30 days
- 31 to 45 days
- 46 to 60 days
- 61 to 75 days

- 76 to 90 days
- 91 to 105 days
- > 105 days

In addition, the number and percentage of subjects with study drug duration of ≥ 52 days for Arm A, ≥ 77 days for Arm B and ≥ 103 days for Arm C will be summarized.

9.2 Compliance

For each kit, the total number of tablets dispensed and returned is recorded. The compliance for study drug (glecaprevir/pibrentasvir) during the Treatment Period will be calculated as the percentage of tablets taken relative to the total tablets expected to be taken. The total number of tablets expected to be taken will be equal to the total number of tablets that should have been taken per the protocol for the duration that the subject was in the Treatment Period (date of last dose of study drug – date of first dose of study drug + 1). Study drug interruptions recorded on the eCRF will not be subtracted from the duration.

A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum by treatment arm. A listing of compliance for each subject will be provided. The percentage of compliant subjects will be summarized for each treatment arm based on data as observed.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

All efficacy analyses will be performed on the ITT population, unless otherwise specified.

Missing data will be imputed as described in Section 6.3 for analyses of the HCV RNA endpoints of SVR.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for this assay (regardless of genotype) are both 15 IU/mL.

HCV RNA results that are detectable but not quantifiable are reported as "< 15 IU/ML HCV RNA DETECTED" and those that are undetectable are reported as "HCV RNA NOT DETECTED" in the database.

The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 15 IU/mL, including values reported as "HCV RNA NOT DETECTED" or "< 15 IU/ML HCV RNA DETECTED." HCV RNA \geq LLOQ are all quantifiable values of 15 IU/mL or greater.

Definitions for Efficacy Endpoints

A confirmed quantifiable value during treatment is defined as any two consecutive HCV RNA measurements \geq LLOQ (or 100 IU/mL for **Breakthrough**), either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement. A confirmed quantifiable post-treatment value is defined as any two consecutive post-treatment HCV RNA measurements \geq LLOQ.

Breakthrough = confirmed HCV RNA \geq 100 IU/mL after HCV RNA < LLOQ during the Treatment Period; or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements $> 1 \log_{10}$ IU/mL above nadir) at any time point during the Treatment Period. A single breakthrough value (\geq 100 IU/mL or $> 1 \log_{10}$ above nadir) followed by lost to follow-up also will be considered a breakthrough (i.e., will not require confirmation).

EOT failure = HCV RNA \geq LLOQ at end of treatment with at least 6 weeks of treatment, where the HCV RNA value must be collected on or after Study Drug Day 36 and study drug duration \geq 36 days.

On-treatment virologic failure = Breakthrough or EOT failure; if a subject meets both definitions of Breakthrough and EOT failure, he or she will be categorized as Breakthrough only.

SVR₄ = HCV RNA < LLOQ in the SVR₄ window (4 weeks after the last actual dose of active study drug) without any confirmed quantifiable (\geq LLOQ) post-treatment value before or during that SVR window.

SVR₁₂ = HCV RNA < LLOQ in the SVR₁₂ window (12 weeks after the last actual dose of active study drug) without any confirmed quantifiable (\geq LLOQ) post-treatment value before or during that SVR window.

SVR₂₄ = HCV RNA < LLOQ in the SVR₂₄ window (24 weeks after the last actual dose of active study drug) without any confirmed quantifiable (\geq LLOQ) post-treatment value before or during that SVR window.

Relapse₁₂ = confirmed HCV RNA \geq LLOQ between end of treatment and 12 weeks after last actual dose of active study drug (up to and including the SVR₁₂ window) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment, excluding reinfection as described below.

Relapse₂₄ = confirmed HCV RNA \geq LLOQ within the SVR₂₄ window for a subject who achieved SVR₁₂ and has HCV RNA data available in the SVR₂₄ window, excluding reinfection.

Relapse_{overall} = confirmed HCV RNA \geq LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the PT Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment, excluding reinfection.

Virologic failure for SVR₁₂ = On-treatment virologic failure or Relapse₁₂

Only subjects who have at least one post-treatment HCV RNA value will be included in analyses of relapse. For the analysis of relapse, completion of treatment is defined as a study drug duration of 52 days or greater for Arm A, 77 days or greater for Arm B, and 103 days or greater for Arm C. If the last available post-treatment value is \geq LLOQ, then the subject will be considered a relapse (i.e., will not require confirmation).

HCV reinfection is defined as confirmed HCV RNA \geq LLOQ after the end of active treatment in a subject who had HCV RNA $<$ LLOQ at Final Treatment Visit, along with the post treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis of the NS3 or NS5A, and/or NS5B gene sequences. Reinfection in the case of the same HCV subtype is defined as a clade switch, as indicated by the lack of clustering between the baseline and post-treatment sequences by phylogenetic analysis. If phylogenetic analysis is not possible due to technical difficulties, HCV reinfection may be determined with a confirmed HCV genotype or subgenotype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Post-treatment relapse is defined as described earlier (**Relapse₁₂**, **Relapse₂₄**, **Relapse_{overall}**), and no genotype, subtype, or clade switch compared with baseline as determined by phylogenetic analysis of the NS3 or NS5A gene sequences. If phylogenetic analysis is not possible due to technical difficulties, the subject will be defined as having a post-treatment relapse unless an HCV genotype or subtype switch is confirmed by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Reasons for SVR₁₂ Non-Response

Subjects who do not achieve SVR₁₂ (SVR₁₂ non-responders) will be categorized as having:

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. HCV reinfection (see definition described earlier);
3. Relapse₁₂;

4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR₁₂ non-responder who prematurely discontinued study drug [study drug duration < 52 days for Arm A, < 77 days for Arm B, and < 103 days for Arm C] and did not meet the **On-treatment virologic failure or reinfection** definitions);
5. Missing follow-up data in the SVR₁₂ window (defined as any subject who completed study drug without data in the SVR₁₂ window after applying the imputation rules and not meeting the definitions of [1], [2], [3], or [4]);
6. Other (defined as any SVR₁₂ non-responder not meeting the definitions of [1] – [5]).

Reasons for SVR₂₄ Non-Response

Subjects who do not achieve SVR₂₄ (SVR₂₄ non-responders) will be categorized as having:

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. HCV reinfection;
3. Relapse₁₂;
4. Relapse₂₄;
5. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR₂₄ non-responder who prematurely discontinued study drug [study drug duration < 52 days for Arm A, < 77 days for Arm B, and < 103 days for Arm C] and did not meet the **On-treatment virologic failure, HCV reinfection, Relapse₁₂, or Relapse₂₄** definitions);
6. Missing follow-up data in the SVR₂₄ window (defined as any subject who completed study drug without data in the SVR₂₄ window after applying the imputation rules and not meeting the definitions of [1], [2], [3], [4], or [5]);

7. Other (defined as any SVR₂₄ non-responder not meeting the definitions of [1] – [6]).

For the reasons for SVR₁₂ and SVR₂₄ nonresponse defined above, subjects are only to be counted in 1 category. Specifically, subjects who were SVR₁₂ or SVR₂₄ nonresponders meeting the definition of HCV reinfection will be counted in the reinfection category regardless of whether they meet the definition of prematurely discontinued study drug, relapse₁₂ or relapse₂₄.

10.2 Handling of Multiplicity

There will be no hypothesis testing for the primary and secondary efficacy endpoints. Therefore, there will be no adjustment for multiple comparisons.

10.3 Primary Efficacy Analysis

The primary efficacy endpoint is the percentage of subjects who achieve SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) based on the overall ITT population across treatment durations, genotypes, and cirrhosis status. The number and percentage of subjects achieving SVR₁₂ will be calculated along with a two-sided 95% CI using the normal approximation to the binomial distribution, unless the number of SVR₁₂ non-responders is less than 5, where the Wilson's score method¹ will be used to calculate the CI instead.

A summary of the reasons for SVR₁₂ non-response (e.g., on-treatment virologic failure, relapse, other) will be provided.

10.4 Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- The percentage of subjects with HCV on-treatment virologic failure, and
- The percentage of subjects with Relapse₁₂.

For on-treatment virologic failure and post-treatment relapse, the number and percentage of subjects will be calculated along with a two-sided 95% CI using Wilson's score method for the overall ITT population.

10.5 Sensitivity Analyses for SVR

As sensitivity analyses, the number and percentage of subjects in the mITT-VF population achieving SVR₁₂, as applicable, will be summarized along with a two-sided 95% CI using the normal approximation and a two-sided 95% CI using the Wilson's score method.

The two-sided 95% CI using Wilson's score method will also be calculated as a sensitivity analysis for the primary endpoint of SVR₁₂ based on the ITT population.

A listing of subjects excluded from mITT-VF population will be provided.

10.5.1 Imputation Approaches

No imputation methods will be employed other than those described in Section 6.3.

10.6 Efficacy Subgroup Analysis

The percentage of subjects with SVR₁₂ in the ITT population will be calculated with the corresponding two sided 95% Wilson score intervals, for the following subgroups:

- HCV genotype and available subtype (based on final HCV genotype and subtype determination);
- Prior HCV treatment history (TN or TE);
- For TE subjects, type of previous regimen (IFN- or SOF-based);
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Sex (male or female);
- Race (White, Black/African-American, Asian, or other) and black race: black or non-black;
- Baseline BMI (< 30, or ≥ 30 kg/m²);

- Baseline HCV RNA level ($< 1,000,000$; $\geq 1,000,000$ to $< 2,000,000$; or $\geq 2,000,000$ IU/mL);
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, or F4);
- Baseline cirrhosis Status (yes/no)
- Baseline platelet count (< 90 or $\geq 90 \times 10^9/L$);
- Baseline albumin (< 35 or ≥ 35 g/L);
- History of diabetes (yes/no);
- Subject on stable opiate substitution (yes/no);
- For dialysis subjects, dialysis type (hemodialysis, peritoneal dialysis, or other);
- Chronic kidney disease stage at screening (Stage 3b, 4, 5 without dialysis, or 5 requiring dialysis);
- Baseline polymorphisms in NS3 and/or NS5A.

The presence of baseline polymorphisms in the above listed subgroup analyses is defined in Section 10.8.1.

10.7 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized for the ITT population:

- The percentage of subjects with HCV RNA $< \text{LLOQ}$ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects with SVR_4 ;
- The percentage of subjects with SVR_{24} ;
- The percentage of subjects who relapsed after achieving SVR_{12} (**Relapse₂₄**).
- The percentage of subjects with virologic failure through Post-Treatment Week 12 (i.e., the SVR_{12} non-responders due to on-treatment virologic failure or Relapse_{12})

The number and percentage of subjects meeting each additional efficacy endpoint will be calculated along with a two-sided 95% CI using the Wilson's score method. Imputations for missing data will be performed as described in Section 6.3 for analysis of SVR,

virologic failure, and relapse. The first bulleted endpoint above will be presented using data as observed.

A summary of the subjects who completed treatment and relapsed (defined as **Relapse_{overall}**) will be prepared displaying the number of subjects relapsing overall and by SVR visit window (within the SVR₄, SVR₁₂, SVR₂₄ windows or after SVR₂₄ window), including the subject number and the SVR visit window corresponding to the first HCV RNA value of those indicating the occurrence of relapse. A similar summary will be prepared for subjects who prematurely discontinued treatment and relapsed after having HCV RNA < LLOQ at their Final Treatment Visit. A listing of subjects in the ITT population excluded from the relapse denominator (e.g., study drug duration < 52 days for subjects assigned to 8 weeks of treatment) will be provided, as applicable.

A listing of subject numbers and reasons for non-response to SVR₁₂ will be prepared. A similar summary and listing will be prepared for subjects who do not achieve SVR₂₄ (as defined in Section 10.1).

The concordance between SVR₁₂ and SVR₂₄ will be assessed by the agreement between SVR₁₂ and SVR₂₄ and the positive predictive value (PPV) and negative predictive value (NPV) of SVR₁₂ on SVR₂₄. The agreement between SVR₁₂ and SVR₂₄ is a percentage defined as the number of subjects achieving both SVR₁₂ and SVR₂₄ and the number of subjects where both SVR₁₂ and SVR₂₄ are not achieved. The PPV of SVR₁₂ on SVR₂₄ is the proportion of subjects who achieve SVR₂₄ out of all subjects who achieved SVR₁₂. The NPV of SVR₁₂ on SVR₂₄ is the proportion of subjects who do not achieve SVR₂₄ out of all subjects who did not achieve SVR₁₂.

10.8 Resistance Analyses

For all subjects, full length NS3/4A and NS5A from baseline samples will be sequenced by next generation sequencing (NGS). For subjects who experience virologic failure (on-treatment virologic failure or post-treatment relapse as defined in Section 10.1), full length NS3/4A and NS5A from the first sample after virologic failure with HCV RNA

≥ 1000 IU/mL will be sequenced by NGS. Subjects treated with study drug who do not achieve SVR₁₂ due to reasons other than virologic failure (i.e., prematurely discontinued study drug with no on-treatment virologic failure, HCV reinfection, missing SVR₁₂ data or other reasons as described in Section 10.1, Reasons for SVR₁₂ Non-Response), but have a time point with HCV RNA ≥ 1000 IU/mL after treatment discontinuation, will have the sample at that time point sequenced.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of HCV virologic failure or treatment discontinuation is < 1000 IU/mL, the sample closest in time after HCV virologic failure/treatment discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used.

For each DAA target, signature amino acid positions and a key subset of amino acid positions for the respective inhibitor class are listed in Table 8. Appropriate subtype-specific prototypic reference sequence will be used for comparison with sequences from samples.

Table 8. Signature Amino Acid Positions and the Key Subset of Amino Acid Positions

| Target | Signature Amino Acid Positions | Key Subset of Amino Acid Positions |
|----------------------|---|--------------------------------------|
| GT1 NS3 | 36, 43 (GT1a only), 54, 55, 56, 80, 107, 122, 132 (GT1a only), 155, 156, 158, 168, 170, 175 (GT1b only) | 155, 156, 168 (all GTs) |
| GT2, 3, 4, 5, 6 NS3 | 36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3-only), 168 | |
| GT1 NS5A | 24, 28, 29, 30, 31, 32, 54 (GT1b only), 58, 62, 92, 93 | 24, 28, 30, 31, 58, 92, 93 (all GTs) |
| GT2, 3, 4, 5, 6 NS5A | 24, 28, 29, 30, 31, 32, 58, 92, 93 | |

Included time points for analyses on samples from subjects who do not achieve SVR₁₂ are 1) the sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1000 IU/mL, and 2) 24 weeks post-DAA treatment, provided that resistance-associated

variants were detected by NGS at the time of HCV virologic failure/treatment discontinuation.

The following definitions will be used in the resistance analyses:

- Baseline polymorphism: a polymorphism by NGS in a baseline sample ($\geq 2\%$ or $\geq 15\%$ prevalence within a subject's viral population depending on polymorphism frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3/4A or NS5A).
- Polymorphism/substitution at a signature amino acid position: polymorphism (relative to reference) present in a baseline sample or substitution (relative to baseline) present in post-baseline sample at a signature amino acid position.
- Post-baseline substitution: an amino acid substitution in a post-baseline time point sample that was not detected at baseline ($< 2\%$) in the subject and is detectable in $\geq 2\%$ of the sequences from the post-baseline sample.
- Enriched polymorphism: polymorphism present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20]
- Treatment-emergent substitution: A post-baseline substitution or an enriched polymorphism.

Analysis 1: The following analyses will be provided for all subjects, separated by Arm, HCV subtype, and treatment experience (treatment-naïve or treatment-experienced, and overall):

- A listing of all subjects with baseline polymorphisms (2% detection threshold) at signature amino acid positions for each DAA target (NS3/4A and NS5A).
- A listing of all subjects with baseline polymorphisms (15% detection threshold) at non-signature amino acid positions for each DAA target (NS3/4A and NS5A) for subjects who experience virologic failure.

- A by-subject listing of baseline polymorphisms (15% detection threshold) at signature amino acid positions in subjects with polymorphisms across both NS3 and NS5A, or those with multiple baseline polymorphisms within any one target (NS3/4A or NS5A).
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15%.
- Total number and percentage of subjects with baseline polymorphisms at a key subset of amino acid positions in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A, by subtype, and total (include all subtypes).

Analysis 2: The impact of baseline polymorphisms on treatment outcome will be assessed as follows: for each polymorphism, the SVR₁₂ rate will be calculated for subjects with and without the polymorphism and the 2 rates will be compared. Analysis will be grouped by Arm, HCV subtype, treatment experience (treatment-naïve or treatment-experienced, and overall), and DAA target (NS3/4A or NS5A).

The following will be included in the analyses of impact of baseline polymorphisms on treatment outcome:

- For each signature amino acid position, presence of any polymorphism at that position (vs no polymorphism at that position), using detection thresholds of both 2% and 15%.
- Each individual polymorphism at each signature amino acid position (vs not that polymorphism) using detection thresholds of 2% and 15%.
- Polymorphisms at each non-signature amino acid position at a detection threshold of 15%.

Analysis 3: In subjects with or without polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A at the key subset of amino acid positions at 15% detection threshold, the SVR₁₂ rate will be calculated, and the rates with or without polymorphisms will be compared using Fisher's exact test.

Analysis will be separated by Arm, HCV subtype, treatment experience (treatment-naïve or treatment-experienced, and overall). The following tables will be provided:

- Comparison of SVR₁₂ rates by subtype, and total (include all subtypes)
- Comparison of SVR₁₂ rates by genotype, and total (include all subtypes)

Analysis 4: The following analyses will be performed for subjects who do not achieve SVR₁₂ or SVR₂₄, and who have post-baseline resistance data available:

- Listings by subject of all treatment-emergent substitutions relative to the baseline amino acid sequences will be provided for each DAA target (NS3/4A and NS5A).
- Listings by subject and time point of all post-baseline substitution at signature amino acid position relative to the baseline amino acid sequence will be provided for each DAA target (NS3/4A and NS5A).
- The persistence of post-baseline substitutions at signature amino acid positions for each target will be assessed by NGS at Post-Treatment Week 24. A listing by subject and time point of all post-baseline substitutions relative to the baseline amino acid sequence will be provided for each DAA target. If resistance-associated substitutions are not detected in a given target for a subject at the time of failure/discontinuation, then that target may not be sequenced in subsequent samples from that subject.

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV NS3/4A and/or NS5A sequence from baseline samples from all subjects in order to accurately determine genotype/subtype. If the phylogenetic analysis is not available, then the result from Sanger sequencing of a region of NS5B by AbbVie or by the Central laboratory will be used to determine the subject's HCV genotype/subtype, if available. Finally, if neither the phylogenetic analysis result nor the Sanger sequencing assay results is available, then the Inno-LiPA assay results from the Central laboratory will be used to categorize the subject. This information will be presented in summaries of efficacy subgroup analyses.

The baseline characteristic summary will use the results from the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]). A summary of HCV genotype subtype as provided by the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]) versus phylogenetic analysis also will be provided. Listing of HCV genotype and subtype will be provided separately for central laboratory results and phylogenetic analysis results.

10.8.1 Presence of Baseline Polymorphisms for Subgroup Analyses of SVR₁₂

For the efficacy subgroup analyses defined in Section 10.6, any NS3/4A variant and any NS5A variant are defined as follows using the subset of signature amino acid positions of interest for HCV (Table 9), where baseline variants based on $\geq 15\%$ NGS detection threshold are considered.

For example, all HCV genotype 2 subjects with any baseline variant at amino acid positions 155, 156, or 168 will be counted as having any NS3/4A variant at baseline; any HCV genotype 2 subjects with any baseline variant at amino acid positions 24, 28, 30, 92, or 93 will be counted as having any NS5A variant at baseline.

Table 9. Amino Acid Positions for Subgroup Analysis

| Target | Genotype | Subgroup Amino Acid Positions (All Variants at These Positions are to Be Included) |
|--------|------------------|--|
| NS3/4A | 1, 2, 3, 4, 5, 6 | 155, 156, 168 |
| NS5A | 1a | 28, 30, 31, 93, H58D, E62A |
| | 1b | 31, 93 |
| | 2 | 24, 28, 30, 92, 93 |
| | 3 | 24, 28, 30, 31, 58, 93 |
| | 4 | 24, 28, 30, 31, 93 |
| | 5 | 24, 28, 30, 31, 58, 92, 93 |
| | 6 | 24, 28, 30, 31, 58, 92, 93 |

The number and percentage of subjects in the ITT and mITT-VF populations will be summarized for the presence of baseline resistance- associated variants of:

1. Any NS3/4A variant at baseline (yes/no);
2. Any NS5A variant at baseline (yes/no);
3. Any NS3/4A variant at baseline **or** any NS5A variant at baseline (yes/no);
4. Both NS3/4A and NS5A variant at baseline (i.e., any NS3/4A variant at baseline and any NS5A variant at baseline) (yes/no);
5. Presence or absence of any variant
 - 5a. Any NS3/4A variant at baseline only (i.e., without baseline NS5A variants);
 - 5b. Any NS5A variant at baseline only (i.e., without baseline NS3/4A variants);
 - 5c. Both NS3/4A and NS5A variant at baseline;
 - 5d. None (i.e., no baseline variant in either NS3/4A or in NS5A at baseline).

10.9 Patient Reported Outcomes

The Kidney Disease Quality of Life (KDQOL36™) instruments will be used to collect patient reported outcomes (PROs). The KDQOL-36 is a disease specific Quality of Life instrument to be used in patients with chronic kidney disease. The KDQOL-36 consists of 4 subscales aimed at quantifying both general health and disease specific attributes. The subscales include: the Short Form-12 (a general health subscale SF-12), burden of kidney disease, symptoms/problems, and effects of kidney disease. The results of the SF-12 instrument are summarized into the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score. The raw scores are transformed linearly to a range of 0 to 100, with higher scores indicating better health-related Quality of Life.²⁻⁴

Summary statistics for each protocol-specified visit (number of non-missing observations, mean) and for change from baseline to each protocol-specified, post-baseline visit

(number of non-missing observations, mean, standard deviation, minimum, maximum) will be provided for the KDQOL-36 subscale scores (SF-12 summarized by PCS and MCS, burden of kidney disease, symptoms/problems, and effects of kidney disease).

If a subject starts another treatment for HCV, then all PRO values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses.

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will be performed using the safety population. Data will be summarized overall (across all arms).

11.2 Analysis of Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the clinical study report.

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with an onset date that is after the first dose of study drug and no more than 30 days after the last dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. If an incomplete onset date was collected for an AE, the event will be assumed to be treatment-emergent, unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

11.2.2 Tabulations of Treatment-Emergent Adverse Events

The number and percentage of subjects with treatment-emergent AEs will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The SOC will

be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC.

Subjects reporting more than one AE for a given PT will be counted only once for that term (most severe/highest grade incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one AE within a SOC will be counted only once for that SOC. Subjects reporting more than one AE will be counted only once in the overall total.

Adverse Event Overview

An overview of AEs will be presented, consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE;
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Treatment-emergent AEs of grade 3 or higher;
- Treatment-emergent AEs of grade 3 or higher with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Treatment-emergent AEs leading to discontinuation of study drug;
- DAA-related treatment-emergent AEs leading to discontinuation of study drug;
- Serious treatment-emergent AEs leading to discontinuation of study drug;
- Treatment-emergent AEs leading to interruption of study drug;
- Treatment-emergent AEs leading to death;
- Deaths.

Adverse Events by SOC and PT

The following summaries of AEs by SOC and PT will be generated by treatment arm and overall:

- Treatment-emergent AEs;
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Treatment-emergent AEs of grade 3 or higher;
- Treatment-emergent adverse events of grade 3 or higher with a "reasonable possibility" of being related to DAA (glecaprevir/pibrentasvir);
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Treatment-emergent AEs leading to discontinuation of study drug;
- DAA-related treatment-emergent AEs leading to discontinuation of study drug;
- Serious treatment-emergent AEs leading to discontinuation of study drug;
- Treatment-emergent AEs leading to interruption of study drug;
- Treatment-emergent AEs leading to death.

A listing of treatment-emergent AEs grouped by SOC and preferred term with subject numbers will be created.

Adverse Events by PT

The number and percentage of subjects experiencing treatment-emergent AEs will be tabulated according to PT and sorted by overall frequency in the safety population. Similar summaries will be provided for grade 3 or higher treatment emergent AEs, DAA-related treatment-emergent AEs, DAA-related grade 3 or higher treatment-emergent AEs, and DAA-related treatment-emergent serious AEs.

Adverse Events by Maximum Severity Grade Level

Treatment-emergent AEs and DAA-related treatment-emergent AEs will be summarized by maximum severity grade level of each preferred term. Each AE will be assigned a grade level (grade 1, 2, 3, 4, or 5) by the investigator. If a subject has an AE with unknown severity, then the subject will be counted in the severity grade level category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same AE with the highest grade level (grade 5). In this case, the subject will be counted under the "Grade 5" category.

Adverse Events by Maximum Relationship

Treatment-emergent AEs also will be summarized by maximum relationship of each preferred term to study drug (DAAs), as assessed by the investigator. If a subject has an AE with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same AE with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

11.2.3 Adverse Events of Special Interest

Adverse events of special interest include the following:

- Hepatic decompensation/hepatic failure events, identified using the AbbVie Product MedDRA Query (PMQ) for Hepatic Decompensation and Hepatic Failure.
- Hepatocellular carcinoma events, identified using the preferred terms of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent.

For the hepatic decompensation/ hepatic failure AE of special interest, the number and percentage of subjects experiencing at least one treatment-emergent AE in the search will

be presented by SOC and preferred term and across all SOC/preferred terms. In addition, a by-subject listing of treatment-emergent AEs meeting the search criterion will be provided.

For the hepatocellular carcinoma AE of special interest, a by-subject listing of all post-baseline (i.e., including both treatment-emergent and non-treatment emergent) AEs meeting the search criterion will be provided.

11.2.4 Listings of Adverse Events

The following listings of AEs will be prepared:

- All serious AEs (from the time the subject signed the study-specific informed consent through the end of the study),
- Treatment-emergent serious AEs,
- Treatment-emergent AEs leading to death,
- Treatment-emergent AEs leading to discontinuation of study drug,
- Treatment-emergent AEs leading to study drug interruption,
- AEs (treatment-emergent or all, as applicable) in each of the AEs of special interest categories.

11.3 Analysis of Laboratory Data

Data collected from the central and local laboratories, including additional laboratory testing due to a serious AE, will be used in all analyses.

11.3.1 Variables and Criteria Defining Abnormality

Hematology variables to be summarized include: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, bands, lymphocytes, monocytes, basophils, eosinophils, platelet count, reticulocyte count, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT).

Chemistry variables to be summarized include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, total protein, glucose, albumin, chloride, bicarbonate, magnesium, gamma-glutamyl transferase (GGT), creatinine clearance (calculated using Cockcroft-Gault), and eGFR by MDRD.

The definitions of toxicity grades for laboratory parameters are presented in [Table 10](#).

Table 10. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

| Test | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---------------------------|-----------------------------------|------------------------------------|------------------------------------|-----------------------------|
| ALT | > ULN – 3 × ULN | > 3 – 5 × ULN | > 5 – 20 × ULN | > 20 × ULN |
| AST | > ULN – 3 × ULN | > 3 – 5 × ULN | > 5 – 20 × ULN | > 20 × ULN |
| Alkaline Phosphatase | > ULN – 2.5 × ULN | > 2.5 – 5 × ULN | > 5 – 20 × ULN | > 20 × ULN |
| Total Bilirubin | > ULN – 1.5 × ULN | > 1.5 – 3 × ULN | > 3 – 10 × ULN | > 10 × ULN |
| Hemoglobin | < LLN – 100 g/L | < 100 – 80 g/L | < 80 g/L | -- |
| Absolute Neutrophil Count | < LLN – 1.5 × 10 ⁹ /L | < 1.5 – 1.0 × 10 ⁹ /L | < 1.0 – 0.5 × 10 ⁹ /L | < 0.5 × 10 ⁹ /L |
| Platelet count | < LLN – 75.0 × 10 ⁹ /L | < 75.0 – 50.0 × 10 ⁹ /L | < 50.0 – 25.0 × 10 ⁹ /L | < 25.0 × 10 ⁹ /L |
| INR | > 1 – 1.5 × ULN | > 1.5 – 2.5 × ULN | > 2.5 × ULN | -- |
| Creatinine clearance | < LLN – 60 mL/min | < 60 – 30 mL/min | < 30 – 15 mL/min | < 15 mL/min |
| Albumin | < LLN – 30 g/L | < 30 – 20 g/L | < 20 g/L | -- |
| White blood cells | < LLN – 3.0 × 10 ⁹ /L | < 3.0 – 2.0 × 10 ⁹ /L | < 2.0 – 1.0 × 10 ⁹ /L | < 1.0 × 10 ⁹ /L |
| Lymphocyte | < LLN – 0.8 × 10 ⁹ /L | < 0.8 – 0.5 × 10 ⁹ /L | < 0.5 – 0.2 × 10 ⁹ /L | < 0.2 × 10 ⁹ /L |
| GGT | > ULN – 2.5 × ULN | > 2.5 – 5 × ULN | > 5 – 20 × ULN | > 20 × ULN |
| Glucose (high) | > ULN – 8.9 mmol/L | > 8.9 – 13.9 mmol/L | > 13.9 – 27.8 mmol/L | > 27.8 mmol/L |
| Glucose (low) | < LLN – 3.0 mmol/L | < 3.0 – 2.2 mmol/L | < 2.2 – 1.7 mmol/L | < 1.7 mmol/L |
| Creatinine | > ULN – 1.5 × ULN | > 1.5 – 3 × ULN | > 3 – 6 × ULN | > 6 × ULN |
| aPTT | > ULN – 1.5 × ULN | > 1.5 – 2.5 × ULN | > 2.5 × ULN | -- |
| Sodium (low) | < LLN – 130 mmol/L | -- | < 130 – 120 mmol/L | < 120 mmol/L |
| Sodium (high) | > ULN – 150 mmol/L | > 150 – 155 mmol/L | > 155 – 160 mmol/L | > 160 mmol/L |
| Potassium (low) | < LLN – 130 mmol/L | -- | < 130 – 120 mmol/L | < 120 mmol/L |
| Potassium (high) | > ULN – 5.5 mmol/L | > 5.5 – 6.0 mmol/L | > 6.0 – 7.0 mmol/L | > 7.0 mmol/L |
| Magnesium (low) | < LLN – 0.5 mmol/L | < 0.5 – 0.4 mmol/L | < 0.4 – 0.3 mmol/L | < 0.3 mmol/L |
| Magnesium (high) | > ULN – 1.23 mmol/L | -- | > 1.23 – 3.30 mmol/L | > 3.30 mmol/L |

11.3.2 Statistical Methods

The baseline value for clinical laboratory tests will be the last non-missing measurement on or before the day of the first dose of study drug. Values on Day 1 must also be before

the time of first dose if time is available. The same baseline value will be used for changes at Treatment Period visits and changes at Post-Treatment Period visits.

Changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized. Each protocol-specified laboratory parameter will be summarized with the sample size, baseline mean; visit mean; and change from baseline mean, standard deviation, minimum, median, and maximum.

Individual changes in the laboratory parameters listed in Section 11.3.1 will be tabulated using shift tables. Laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used for each sample. Shift tables from baseline to minimum value and maximum value during the Treatment Period will be created. For each parameter, the shift tables will cross tabulate the frequency of subjects with baseline values below/within the normal range to maximum above the normal range and with baseline values within/above the normal range to minimum below the normal range.

The laboratory parameters listed in Table 10 will be assigned a toxicity grade of 1, 2, 3, or 4. The number and percentage of subjects with a maximum toxicity grade of 1, 2, 3 or 4 will be tabulated. To be counted, the post-baseline value must have a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value. For each laboratory parameter in Table 10, the summary will also include the number and percentage of subjects with a maximum of at least grade 3. A listing of all relevant laboratory parameters will be provided for each subject who had an increase to grade 2 or higher for any laboratory variable in Table 10.

For CKD 3B and 4 subjects at screening, laboratory calculated eGFR by MDRD at Screening, EOT, and Post Treatment Week 4 will be summarized by mean, sd, minimum, maximum, median and interquartile range as well as by a box-plot.

CKD categorization at EOT is defined according to eGFR and requirement of dialysis in Table 4. For CKD 3B and 4 subjects at screening, number and percentage of subjects

changing in CKD stage (improvement, no change, or decline) between screening and EOT will also be summarized and graphed by treatment arm. For CKD 3B and 4 subjects at screening, a listing will be provided for subjects with CKD stage worsening based on any eGFR criteria or initiated dialysis treatment during the treatment and post treatment period. A separate listing will also be provided for subjects not on dialysis prior to screening while started dialysis post screening.

Assessment of Hepatic Laboratory Values

The number and percentage of subjects with laboratory values meeting the following criteria during treatment will be summarized:

- Post-nadir (preceding value is lower than the subsequent value) ALT $> 5 \times \text{ULN}$ (regardless of grade change);
- Total bilirubin $\geq 2 \times \text{ULN}$ and $>$ baseline (i.e., a post-baseline value must be more extreme than the baseline value to be considered);
- Post-nadir ALT $> 3 \times \text{ULN}$ and total bilirubin $> 2 \times \text{ULN}$;
- Post-nadir ALT $> 3 \times \text{ULN}$ and total bilirubin $\leq 2 \times \text{ULN}$.

Four listings (one for each bullet above) of all liver function tests including ALT, AST, total, indirect and direct bilirubin, ratio of direct to total bilirubin, and alkaline phosphatase values will be provided for each subject who met the criterion defined above.

Hepatic Laboratory Abnormalities of Interest

Among the events assessed under "Assessment of Hepatic Laboratory Values," the following criteria are of interest:

- Confirmed post-nadir ALT $> 5 \times \text{ULN}$;
- Post-nadir ALT $> 3 \times \text{ULN}$ and a concurrent total bilirubin $> 2 \times \text{ULN}$ with a direct bilirubin:total bilirubin ratio > 0.4 .

To support the assessment of hepatic laboratory abnormalities of interest, the following potential events will be summarized:

- Confirmed post-nadir $ALT > 5 \times ULN$;
- Post-nadir $ALT > 3 \times ULN$ and total bilirubin $> 2 \times ULN$ and direct/total bilirubin ratio > 0.4 .

Two listings (one for each bullet) of all liver function tests including ALT, AST, total, indirect and direct bilirubin, ratio of direct to total bilirubin, and alkaline phosphatase values will be provided for each subject who met the criterion defined above.

For the **assessments of hepatic laboratory values** and **hepatic laboratory abnormalities of potential interest**, the maximum ratio relative to the ULN will be used to determine if subjects meet any of the criteria listed above. The ALT and total bilirubin values do not need to be concurrent in order to meet the defined criteria in statistical summaries. For ALT, the post-baseline value must represent an increase from the first nadir (including baseline) to be counted. First nadir is defined as the last value prior to the first increase. For total bilirubin, a subject will be counted if the post-baseline laboratory value meets the above criteria regardless of the baseline laboratory value (i.e., the post-baseline laboratory value does not need to be worse than the baseline laboratory value), except where noted above. A confirmed post-nadir increase in ALT is defined as two consecutive values of $ALT > 5 \times ULN$ after nadir, either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement. A single post-nadir ALT value of greater than $5 \times ULN$ followed by lost to follow-up (no additional ALT values) also will be considered (i.e., will not require confirmation). The ratio of direct to total bilirubin will be calculated using the same date/time sample corresponding to the total bilirubin elevation.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

Vital sign variables are body temperature, sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse rate, and body weight.

The criteria for potentially clinically significant (PCS) vital sign findings are presented in [Table 11](#).

Table 11. Criteria for Potentially Clinically Significant Vital Sign Values

| Test/Measurement | Very Low (VL) | Very High (VH) |
|--------------------------|---|--|
| Systolic Blood Pressure | ≤ 90 mmHg AND A decrease of ≥ 20 mmHg from baseline | ≥ 180 mmHg AND An increase of ≥ 20 mmHg from baseline |
| Diastolic Blood Pressure | ≤ 50 mmHg AND A decrease of ≥ 15 mmHg from baseline | ≥ 105 mmHg AND An increase of ≥ 15 mmHg from baseline |
| Pulse Rate | ≤ 50 bpm AND A decrease of ≥ 15 bpm from baseline | ≥ 120 bpm AND An increase of ≥ 15 bpm from baseline |
| Weight | A decrease of $\geq 15\%$ from baseline | An increase of $\geq 15\%$ from baseline |
| Body Temperature | | $> 38.3^{\circ}\text{C}$ AND An increase of $\geq 1.1^{\circ}\text{C}$ from baseline |

11.4.2 Statistical Methods

The baseline value for vital signs will be the last measurement on or before the day of the first dose of study drug. The same baseline value will be used for changes at Treatment Period visits and changes at Post-Treatment Period visits.

Changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized. Each vital sign parameter will be summarized with the baseline mean; visit mean; and change from baseline mean, standard deviation, minimum, median, and maximum.

The number and percentage of subjects with on-treatment values meeting the specified criteria for PCS vital sign values (Table 11) will be summarized. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A separate listing will be provided that presents all vital sign values for the subjects meeting PCS criteria during treatment.

11.5 Analysis of Child-Pugh Score

For subjects with compensated cirrhosis, Child-Pugh scores will be categorized as 5, 6, > 6, or missing at baseline and each protocol-specified post-baseline visit, including applicable post-treatment visits. Shift tables from baseline to each post-baseline visit will be created for the cirrhotic subjects in the safety population. The shift tables will cross-tabulate the frequency of subjects with baseline values in each category versus the post-baseline categories. For each baseline category and across the baseline categories, the percentage of subjects in each post-baseline category (excluding the post-baseline category of missing) will be calculated.

12.0 Summary of Changes

12.1 Summary of Changes Between the Latest Version of the Protocol and SAP

13.0 References

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.
2. Hays RD, Kallich JD, Mapes DL, et al. Development of the kidney disease quality of life (KDQOL) instrument. Qual Life Res. 1994;3(5):329-38.
3. Hays RD, Kallich JD, Mapes DL, et al. Kidney disease quality of life short form (KDQOL-SFTM), version 1.3: a manual for use and scoring. Washington, DC: RAND; 1997.

4. Ware JE, Kosinski M, Keller SD. SF-12: How to score the SF-12 physical and mental health summary scales. Boston, MA: The Health Institute, New England Medical Center, Second Edition, 1995.

Document Approval

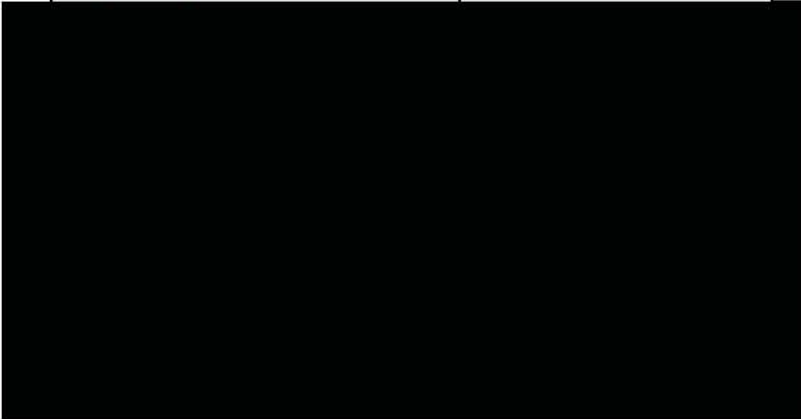
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