1.0 Title Page

Statistical Analysis Plan

Study M16-135

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

Date: 08 Aug 2018

Version 2.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by AbbVie Statistics and Statistical Programming for Study M16-135.

Study M16-135 examines the efficacy and safety of glecaprevir (GLE)/pibrentasvir (PIB) in treatment naïve adults with chronic Hepatitis C Virus (HCV) Genotype (GT) 1 - 6 infection and compensated cirrhosis.

This SAP (Version 2.0) incorporates Version 1.0 of the SAP dated 02 December 2017 and provides details to further elaborate statistical methods as outlined in Clinical Study Protocol M16-135 Amendment 3 dated 11 June 2018, and describes analysis conventions to guide the statistical programming work for the first analysis (after all HCV GT 1, 2, 4, 5 and 6-infected subjects reach Post-Treatment [PT] Week 12 or discontinue the study), the second analysis (after all HCV GT3-infected subjects reach PT Week 12 or discontinue the study), and the end of study analysis (after all subjects reach PT Week 24 or prematurely discontinue from the study). Analyses will be performed using SAS Version 9.3 (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 compare the SVR_{12} rates (12-week sustained virologic response, SVR_{12} [HCV ribonucleic acid {RNA} < lower limit of quantification {LLOQ} 12 weeks following treatment]) of 8 weeks of treatment with the GLE/PIB combination regimen to the historical SVR_{12} rate of 12 weeks of treatment with GLE/PIB in treatment naïve adults with chronic HCV infection and compensated cirrhosis and to assess the safety of 8 weeks of treatment with the GLE/PIB combination regimen in treatment naïve adults with chronic HCV infection and compensated cirrhosis.

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

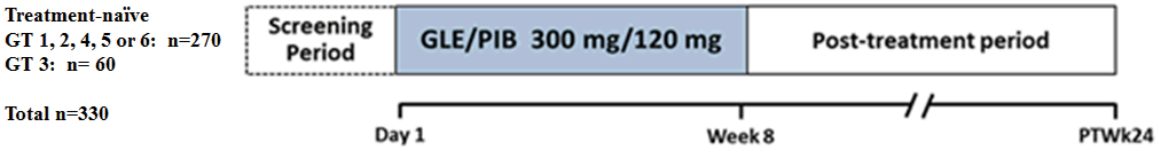
4.2 Design Diagram

This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of 8 weeks of GLE/PIB in HCV treatment-naïve adult subjects with chronic HCV GT 1 - 6 infection and compensated cirrhosis. The study will initially enroll subjects with HCV GT 1, 2, 4, 5 and 6 infection followed by subjects with HCV GT3 infection.

This study consists of a Screening Period, a Treatment Period, and a Post-Treatment (PT) Period.

The study is designed to enroll approximately 330 subjects (approximately 270 with GT1, 2, 4, 5, or 6 infection and approximately 60 with GT3 infection) to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with scientific and ethical considerations.

Figure 1. Study Schematic



4.3 Sample Size

It is planned to enroll approximately 330 adult subjects with chronic HCV GT 1 - 6 infection with compensated cirrhosis who are HCV treatment-naïve in this study.

The study was initially designed to enroll about 270 non-GT3-infected subjects and amended to include GT3-infected subjects for a total of 330 GT1 - 6-infected (270 non-GT3 and 60 GT3) subjects.

With approximately 270 subjects with HCV GT 1, 2, 4, 5, or 6 infection, this study has approximately 91% power to demonstrate efficacy of the 8-week treatment arm compared

to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 94%) based on the Per-Protocol (PP) population, assuming that 98% of the GT1, 2, 4, 5, and 6-infected subjects receiving 8 weeks of treatment in the PP population achieve SVR_{12}.

With approximately 270 subjects with HCV GT 1, 2, 4, 5, or 6 infection, this study has approximately 82% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 93%) based on the ITT population, assuming that 97% of the GT1, 2, 4, 5, and 6-infected subjects receiving 8 weeks of treatment in the ITT population achieve SVR_{12}.

With approximately 330 subjects with HCV GT 1 - 6 infection, this study has approximately 90% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 94%) based on the PP population, assuming that 98% of the GT1 - 6-infected subjects receiving 8 weeks of treatment in the PP population achieve SVR_{12}.

With approximately 330 subjects with HCV GT 1 - 6 infection, this study has approximately 81% power to demonstrate efficacy of the 8-week treatment arm compared to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 93%) based on the ITT population, assuming that 97% of the GT1 - 6-infected subjects receiving 8 weeks of treatment in the ITT population achieve SVR_{12}.

4.3.1 Justification of Primary Endpoint Success Criteria

Efficacy for the 8-week regimen in this study is established by comparing the SVR_{12} rate to the historical control regimen of GLE/PIB administered for 12 weeks. The SVR_{12} rate of the historical control regimen is calculated, and a threshold is determined by subtracting a margin of 6% from the historical SVR_{12} rate. Efficacy is established if the lower 95% confidence bound of the SVR_{12} rate in the 8-week regimen is greater than the threshold.

A margin of 6% is selected to be used in this study to ensure a minimal loss of efficacy of the 8-week arm relative to the historical SVR_{12} rate for the 12-week treatment regimen.

In the registrational program, 117 treatment naïve, HCV GT 1, 2, 4, 5, or 6 subjects with compensated cirrhosis and 65 treatment naïve, GT3-infected subjects with compensated cirrhosis were treated with GLE/PIB for a planned duration of 12 weeks. Three subjects did not achieve SVR_{12}, one discontinued treatment early and two had missing SVR_{12} data. No virologic failure was observed among these subjects, which means that the SVR_{12} rate based on the PP population is 100%. Hence, for this study it assumes that the historical SVR_{12} rate for GT 1 - 6-infected cirrhotic subjects is 100%. To establish the efficacy compared to the historical control, a margin of 6% is applied to the historical control rate of 100%, resulting in a threshold of 94%.

Historical SVR rate based on ITT population depends on the number of non-virologic failures in a study. Study-to-study variability has been observed in non-virologic failure rates, and is typically around 1%. The observed rate of non-virologic failures in the registrational program was 1.2% (29/2369). For this reason, this study assumes that the historical SVR_{12} rate based on ITT population for cirrhotic subjects is 99% (with 1% non virologic failure). To establish the efficacy compared to the historical control, a margin of 6% is applied to the historical control rate of 99%, resulting in a threshold of 93%.

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

4.4.1 Futility Analysis

Study M16-135 is the first study to evaluate GLE/PIB for 8 weeks in treatment-naïve HCV GT 1 - 6-infected subjects with compensated cirrhosis. For that reason, virologic

futility rules are used in the protocol to minimize exposure to a potentially suboptimal duration. The protocol described the futility rules as follows (Protocol Section 5.4.1.2, Treatment Extension Criteria):

> In subjects with GT 1, 2, 4, 5, or 6 infection, an efficacy assessment will evaluate the post-treatment relapse rate when the first 30 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all GT 1, 2, 4, 5, or 6-infected subjects or for a particular subgroup of GT 1, 2, 4, 5, or 6-infected subjects who are on treatment or have completed treatment within the previous 7 days.
>
> The enrollment of additional GT 1, 2, 4, 5, or 6-infected subjects in this study will be terminated if extension of treatment is needed for all GT 1, 2, 4, 5, or 6-infected subjects. If the extension is needed for a particular subgroup of GT 1, 2, 4, 5, or 6-infected subjects, then the enrollment will be terminated for this particular subgroup but other subgroups will continue to be allowed to enroll in the study with 8 weeks treatment duration.
>
> In subjects with GT3 infection, an efficacy assessment will evaluate the post-treatment relapse rate after the first 20 subjects reach Post-Treatment Week 4 and will be done periodically thereafter. If more than 10% of subjects experience post-treatment relapse, an analysis will be conducted to determine if extension of treatment to 12 weeks is needed for all GT3-infected subjects or for a particular subgroup of GT3-infected subjects who are on treatment or have completed treatment within the previous 7 days.
>
> The enrollment of additional GT3-infected subjects in this study will be terminated if extension of treatment is needed for all GT3-infected subjects. If the extension is needed for a particular subgroup of GT3-infected subjects, then the enrollment will be terminated for this particular subgroup but other subgroups will continue to be allowed to enroll in the study with 8 weeks treatment duration.

Subjects who experience virologic failure with the GLE/PIB regimen for 8 weeks in Study M16-135 will be allowed to be screened in the AbbVie Study M15-942.

Post-treatment relapse is defined as confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any post-treatment visit, for a subjects who completed treatment (defined as study drug duration ≥ 52 days) and had HCV RNA < LLOQ at final treatment visit, excluding cases of reinfection. HCV reinfection is defined in Section 10.1.

Evaluations of virologic relapse rate will be performed on an ongoing basis until all subjects reach end of treatment. There will be no statistical adjustment employed due to these futility analyses.

4.4.2 Planned Analyses

Analyses will occur after subjects have completed the PT Week 12 Visit or prematurely discontinued study. The first analysis will occur after all HCV GT1, 2, 4, 5, or 6-infected subjects have completed the PT Week 12 Visit or prematurely discontinued from the study. The second analysis will occur after all HCV GT3-infected subjects have completed the PT Week 12 Visit or prematurely discontinued from the study. The third and final analysis will occur after all subjects have completed or prematurely discontinued from the study.

For each analysis, data will be locked after performing appropriate data cleaning.

Results from the SVR_{12} analyses will be described in clinical study report(s) that are planned to be included as part of submissions to regulatory agencies to support possible labeling changes.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

5.1.1 Intention-to-Treat (ITT) Population

Subjects who receive at least one dose of study drug will be included in the ITT population. Efficacy analyses will be performed on the ITT population, unless otherwise specified.

5.1.2 Per Protocol (PP) Population

All subjects who receive at least one dose of study drug, with the exception of subjects who experience breakthrough, or prematurely discontinue treatment prior to Week 8, or have no HCV RNA value in the SVR_{12} visit window or later will be included in the PP population. In other words, the per protocol population includes all subjects in the ITT population, with the exception of subjects who prematurely discontinue prior to Week 8 (subjects with treatment duration < 52 days), subjects who experience virologic failure prior to Week 8 (subjects with **on-treatment virologic failure** before Study Day 52), subjects without virologic failure who have no HCV RNA value in the SVR_{12} visit window or later, and subjects who are SVR_{12} non-responders due to re-infection. Subjects who have HCV GT3 infection will be excluded from the PP analysis of HCV GT1, 2, 4, 5, and 6-infected subjects.

5.1.3 Safety Population

All subjects who receive at least one dose of study drug will be included in the safety population, which will be the same as the ITT population for this study. Safety and demographic analyses will be performed on the safety population.

5.1.4 Modified Intention-to-Treat (mITT) Populations

Sensitivity analyses of SVR_{12} will be performed on the Modified Intention-to-Treat Genotype (mITT-GT) population and Modified Intention-to-Treat Genotype and

Virologic Failure (mITT-GT-VF) population, respectively, as defined below, when applicable.

The mITT-GT population includes subjects who receive at least 1 dose of study drug but excludes the subjects who were enrolled with ineligible genotypes (e.g., GT3 for the group of HCV GT 1, 2, 4, 5 or 6-infected subjects (final HCV genotype as defined in Section 10.8)).

The mITT-GT-VF population includes all subjects in the mITT-GT population defined above by excluding subjects who did not achieve SVR_{12} for reasons other than virologic failure.

5.2 Variables Used for Stratification of Randomization

No stratification is used for this open-label single-arm study.

5.3 Presentation of Summary Tables

All tables (except safety analyses) will present data in separate columns for the GT 1, 2, 4, 5 and 6-infected subjects, GT 3 subjects, and GT 1 - 6 infected subjects, if applicable. Tables of safety analyses will present data by overall for subjects dosed with GLE/PIB for 8 weeks. For the first analysis when only GT 1, 2, 4, 5 and 6 infected subjects have completed the PT Week 12 Visit or prematurely discontinued study, data will be presented in a single column of GT 1, 2, 4, 5 and 6-infected subjects.

If a subset of subjects has treatment extended, the tables will present separate results for subjects assigned to GLE/PIB for 8 weeks (with a possible breakdown for the subset not requiring treatment extension), subjects assigned to GLE/PIB for 12 weeks following treatment extension, and overall.

6.0 Analysis Conventions

6.1 Baseline and Final Value

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 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 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 PT Periods, respectively. All time points and corresponding time windows are defined based on the date/time of blood sample collection.

For safety, laboratory data, resistance, vital signs and PRO measurements, 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 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. The only exception to this is for the SVR windows (e.g., SVR_4, SVR_{12}, and SVR_{24}); for these windows, 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 in analyses. For summaries of shifts from baseline and potentially 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, Resistance Endpoints, Laboratory, Vital Sign Measurements and PRO Instruments (Treatment Period)

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Day 1/Baseline[a]	1[a]	≤ 1[a]
Week 1	7	2 to 10
Week 2	14	11 to 21
Week 4	28	22 to 42
Week 8	56	43 to 70
Week 12[b]	84	71 to 98
Final Treatment Visit[c]	2 to ≤ 2 days after last dose of study drug	

a. Day of first dose of study drug.

b. Week 12 is only applicable for the subjects who meet treatment extension criteria. If the treatment extension criteria are not met, then there will be no Week 12 visit.

c. 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.

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used. PRO instruments are collected at Day 1, Week 2, Week 4, and End of Treatment Visit.

Table 2. Analysis Time Windows for HCV RNA 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 SVR_4, SVR_{12}, and SVR_{24}. Data must also have Study Drug End Day > 2 for all windows. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Table 3. Safety, Laboratory Data (Including FibroTest, APRI, Child-Pugh Score), Resistance, Vital Sign, and PRO Instruments Visit Windows (Post-Treatment Period)

Scheduled Time	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Days 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[a]	> 2 days after last dose of study drug	

a. The last value within the Post-Treatment Period window will be used to define the final post-treatment value. The lower bound of this Final window is Study Drug End Day 3.

Note: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day > 2. Vital signs are collected at every PT visit; hematology, chemistry, urinalysis, and coagulation panels are collected are collected at PTWk4, and not required at PTWk24 but PTDC only if subject discontinued prior to PT Wk4. PRO instruments are collected at PTWk12 and PTWk24 (or PTDC) only. FibroTest, APRI, and Child-Pugh scores are collected at PTWk12 and PTWk24 (or PTDC).

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

The handling of missing data for patient reported outcomes (PROs) will be as follows. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, 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. The Mental and Physical Component Summary measures will not be computed if any domain is missing. The missing items of the FSS questionnaire will be imputed with the average score of the answered items as long as more than 50% of the items on the FSS are answered. For Treatment Satisfaction Questionnaire – Medication (TSQM), no imputation will be performed for missing items.

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

Demographics, baseline characteristics, medical history, and previous, concomitant and post-treatment medications will be summarized for the safety population.

7.1 Demographic and Baseline Characteristics

Categorical demographic and baseline characteristic variables will be summarized with the number and percentage of subjects. 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 variables include age, weight, height, and body mass index (BMI). Categorical demographic variables include sex, race (using categories on the eCRF), black race (black or non-black, black will include any subject who marks 'Black or African American' for race on the Demographics eCRF), ethnicity, age category (< 65 or ≥ 65 years; < 75 or ≥ 75 years), BMI category (< 30, or ≥ 30 kg/m^2), country, and geographic region (North America, Europe, or rest of world [ROW]).

When defining geographic region, sites in the United States, Canada and Puerto Rico will be grouped under North America; sites in Bulgaria, Czech Republic, France, Greece, Hungary, Ireland, Italy, Poland, Portugal, Romania, Russian Federation, Spain, and the

United Kingdom will be grouped under Europe; sites in Israel, Taiwan and Vietnam will be grouped together as ROW.

Continuous baseline characteristics include baseline $\log_{10}$ HCV RNA level, FibroTest score, FibroScan score, creatinine clearance, eGFR, platelet count, albumin, GGT, APRI, FIB-4, AST, ALT, total, direct, and indirect bilirubin for all subjects.

Categorical baseline characteristics include:

- HCV genotype (1, 2, 3, 4, 5, or 6) and available subtype (as determined by the central laboratory);
- HCV genotype (1, 2, 3, 4, 5, or 6) and available subtype (as determined by phylogenetic analysis);
- HCV genotype (1, 2, 3, 4, 5, or 6) and available subtype (final HCV genotype and subtype as defined in Section 10.8);
- IL28B genotype (CC, CT, or TT; CC or non-CC);
- Baseline HCV RNA level (< 800,000 or ≥ 800,000 IU/mL; < 1,000,000 or ≥ 1,000,000 IU/mL);
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L; < 150 or ≥ 150 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Screening Child-Pugh score (5, 6, or > 6);
- Baseline Child-Pugh score (5, 6, or > 6);
- Baseline FibroTest (< 0.75 or ≥ 0.75);
- Baseline APRI (≤ 1, > 1 to ≤ 2, or > 2);
- Baseline FIB-4 (< 1.45, ≥ 1.45 to ≤ 3.25, or > 3.25);
- Baseline AST/ALT ratio (≤ 1 or >1)
- Baseline total bilirubin (< 34.2 or ≥ 34.2 μmol/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, or ≥ 90 mL/min);
- Baseline eGFR (< 60, ≥ 60 to < 90, or ≥ 90 mL/min/1.73 m^2);
- History of diabetes (yes/no);

- Injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no);
- Subject on stable opiate substitution (yes/no);
- Tobacco user (current, former, never, or unknown);
- Alcohol user (current, former, never, or unknown);
- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no).

If the IL28B genotype result is not available from a sample collected during the Screening period, then a result available from a sample collected at any time during the study will be used to summarize IL28B genotype.

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 point assigned for each of the five observed findings as defined in Table 4.

Table 4. Child-Pugh Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/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)

* 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.

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 baseline values of AST, ALT, and platelet count or subjects who are missing age will be excluded from the summary of FIB-4.

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

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

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

History of diabetes will be based on the Medical History (MH) eCRF, as defined in Table 5.

Table 5. Medical History eCRF

	Medical History eCRF	
Subgroup	**Body System**	**Condition/Diagnosis**
Diabetes	Metabolic	Diabetes mellitus

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the CRF. 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.

8.0 Subject Disposition

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

8.1 Disposition of Safety Population

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

- Subjects enrolled in this study;
- 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 PT Period at the time of the planned analysis.

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

The number and percentage of subjects with reported study drug interruptions will be summarized.

Reasons for study drug interruptions will be presented in the CSR listings.

9.0 Study Drug Exposure and Compliance

9.1 Exposure

The duration of exposure to study drug will be summarized 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.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for exposure during the treatment period.

Study drug duration also will be summarized with frequencies and percentages using the following categories:

- 1 to 15 days, 16 to 35 days, 36 to 51 days, ≥ 52 days.

9.2 Compliance

At each visit (starting with the Week 4 visit) during the Treatment Period, the total number of tablets dispensed and returned is recorded. The compliance for study drug (GLE/PIB) 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. The percentage of compliant subjects will be summarized based on data as observed. An additional summary of the percentage of compliant subjects will be provided where subjects who are missing study drug accountability records will be imputed as non-compliant.

10.0 Efficacy Analysis

10.1 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® Quantitative HCV 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 ≥ LLOQ are all quantifiable values of 15 IU/mL or greater.

IL28B rs12979860 will be resulted as C/C, C/T, or T/T by the central laboratory.

Definitions for Efficacy Endpoints

A confirmed quantifiable value during treatment is defined as any two consecutive HCV RNA measurements ≥ 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 ≥ LLOQ.

Breakthrough = confirmed HCV RNA ≥ 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 (≥ 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 ≥ 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 ≥ 36 days.

On-Treatment Virologic Failure = Breakthrough or EOT Failure.

SVR_4 = HCV RNA < LLOQ in the SVR_4 window (4 weeks after the last actual dose of study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

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

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

$Relapse_{12}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment and has post treatment HCV RNA data available, excluding reinfection as described below.

$Relapse_{24}$ = confirmed HCV RNA ≥ LLOQ during SVR_{24} window among subjects who achieved SVR_{12} and have HCV RNA data available during the SVR_{24} window, excluding reinfection as described below.

$Relapse_{overall}$ = confirmed HCV RNA ≥ 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 and has post treatment HCV RNA data available, excluding reinfection as described below.

Only subjects who have at least one post-treatment HCV RNA value will be included in analyses of relapse. For relapse analyses, the completion of treatment is defined as a study drug duration ≥ 52 days for subjects assigned to 8 weeks of treatment. If the regimen is extended to 12 weeks for some subjects, then those subjects will be considered completers if they have a study duration ≥ 77 days. If the last available post-treatment value is ≥ LLOQ, then the subject will be considered a relapse (i.e., will not require confirmation).

HCV reinfection is defined as confirmed HCV RNA ≥ LLOQ after the end of 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 subtype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Post-treatment relapse is defined as described earlier (**$Relapse_{12}$, $Relapse_{24}$, $Relapse_{overall}$**), 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 SVR_{12} Non-Response

Subjects who do not achieve SVR_{12} (SVR_{12} non-responders) will be categorized as having:

1. On-treatment virologic failure (see **On-treatment virologic failure** definition, if a subject meets both definitions of **Breakthrough** and **EOT failure**, he or she will be categorized as **Breakthrough** only);
2. HCV reinfection (see definition described earlier);
3. $Relapse_{12}$ (see **$Relapse_{12}$** definition);
4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{12} non-responder who prematurely discontinued study drug [study drug duration < 52 days for subjects assigned to 8 weeks of treatment, and < 77 days for subjects extended to 12 weeks of treatment] and did not meet the **On-treatment virologic failure** definition);
5. Missing follow-up data in the SVR_{12} window (defined as any subject who completed study drug without data in the SVR_{12} window after applying the imputation rules and not meeting the definitions of [1], [2], [3], or [4]);
6. Other (defined as any SVR_{12} non-responder not meeting the definitions of [1] – [5]).

Reasons for SVR_{24} Non-Response

Subjects who do not achieve SVR_{24} (SVR_{24} non-responders) will be categorized as having:

1. On-treatment virologic failure (see **On-treatment virologic failure** definition, if a subject meets both definitions of **Breakthrough** and **EOT failure**, he or she will be categorized as **Breakthrough** only);
2. HCV reinfection (see definition described earlier);

3. Relapse$_{12}$ (see **Relapse$_{12}$** definition);
4. Relapsed after achieving SVR$_{12}$ (see **Relapse$_{24}$** definition);
5. Prematurely discontinued study drug with no on-treatment virologic failure and no relapse after achieving SVR$_{12}$ (defined as any SVR$_{24}$ non-responder who prematurely discontinued study drug [study drug duration < 52 days for subjects assigned to 8 weeks of treatment, and < 77 days for subjects extended to 12 weeks of treatment] and did not meet the **On-treatment virologic failure** or **Relapse$_{24}$** definitions);
6. Missing follow-up data in the SVR$_{24}$ window (defined as any subject who completed study drug without data in the SVR$_{24}$ window after applying the imputation rules and not meeting the definitions of [1], [2], [3], [4], or [5]);
7. Other (defined as any SVR$_{24}$ non-responder not meeting the definitions of [1] – [6]).

For the reasons for SVR$_{12}$/SVR$_{24}$ nonresponse defined above, subjects are only to be counted in 1 category. For example, the categories of premature discontinuation and reinfection are mutually exclusive. Thus, subjects who are SVR$_{12}$/SVR$_{24}$ nonresponders meeting the definition of HCV reinfection are counted in the reinfection category and not to be counted in any other category (as in the example, even if such a subject who was determined to be a case of reinfection appeared to meet the definition of prematurely discontinued study drug with no on-treatment virologic failure, the subject is to be counted in the reinfection category only).

10.2 Handling of Multiplicity

In order to control the Type I error rate at 0.05, a fixed sequence testing procedure will be used for the two primary and two key secondary efficacy analyses of SVR$_{12}$ as listed below. The fixed-sequence testing procedure will utilize the efficacy endpoint sequence of the first primary analysis followed by the second primary analysis, then the first key secondary analysis, and lastly the second key secondary analysis. For example, only if

success has been demonstrated for the first primary efficacy analysis of SVR_{12} based on the PP population in HCV GT 1, 2, 4, 5 and 6-infected subjects will the testing proceed to the second primary efficacy analysis of SVR_{12} based on the ITT population in HCV GT 1, 2, 4, 5 and 6-infected subjects. And only if success has been demonstrated for the second primary efficacy analysis of SVR_{12} will the testing proceed to the first key secondary efficacy analysis of SVR_{12} based on the PP population in HCV GT 1 - 6-infected subjects, and so on.

The multiplicity controlled efficacy analyses will be tested sequentially in the following order:

1. Primary 1: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the PP population in HCV GT 1, 2, 4, 5 and 6-infected subjects: If this endpoint is statistically significant, then proceed to the following efficacy endpoint. If this endpoint is not statistically significant then stop the testing procedure and declare that no endpoints in the study met statistical significance.
2. Primary 2: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on ITT population in HCV GT 1, 2, 4, 5 or 6-infected subjects: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant on both PP and ITT population in HCV GT 1, 2, 4, 5 or 6-infected subjects. If not, then announce that SVR_{12} endpoint is statistically significant based on only the PP population in HCV GT 1, 2, 4, 5 or 6-infected subjects and stop testing.
3. Key Secondary 1: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on the PP population in HCV GT 1, 2, 3, 4, 5 and 6-infected subjects: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant on both PP and ITT population in HCV GT 1, 2, 4, 5 or 6-infected subjects and on the PP population in HCV GT 1 - 6-infected subjects. If not, then announce that SVR_{12}

endpoint is statistically significant based on only the preceding populations and stop testing.

4. Key Secondary 2: Efficacy of the SVR_{12} rate of 8-week treatment duration compared to the historical 12 week treatment duration based on ITT population in HCV GT 1, 2, 3, 4, 5 or 6-infected subjects: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant on both PP and ITT population in HCV GT 1, 2, 4, 5 or 6-infected subjects and on both the PP and ITT population in HCV GT 1 - 6-infected subjects. If not, then announce that SVR_{12} endpoint is statistically significant based on only the preceding populations and stop testing.

10.3 Primary Efficacy Analysis

The two primary efficacy analyses included in the fixed-sequence testing procedure as described in Section 10.2 are:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT 1, 2, 4, 5 or 6-infected subjects based on the PP population in the 8-week treatment duration achieving SVR_{12} is greater than 94%.
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT 1, 2, 4, 5 or 6-infected subjects based on the ITT population in the 8-week treatment duration achieving SVR_{12} is greater than 93%.

The two primary efficacy analyses will be tested using the hierarchical order outlined above to control the Type I error rate. Only if success has been demonstrated for the first primary efficacy analysis of SVR_{12} based on the PP population in HCV GT 1, 2, 4, 5 or

6-infected subjects, will the testing proceed to the second primary efficacy analysis of SVR_{12} based on the ITT population in HCV GT 1, 2, 4, 5 or 6-infected subjects.

For the first primary efficacy analysis, the PP population (defined in Section 5.1.2) will be used. The PP analysis is used to reduce the risk of bias toward no treatment difference that can occur due to dropouts or other measurement problems, since the subjects excluded in the PP population experience SVR failure for reasons that do not help in discriminating between treatment durations.

For both primary efficacy analyses, the percentage of subjects achieving SVR_{12} and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution, unless the number of subjects who failed to achieve SVR_{12} is less than 5, then the Wilson's score method1 will be used for the confidence interval instead.

10.4 Secondary Efficacy Analyses

10.4.1 Key Secondary Efficacy Analyses

The two key secondary efficacy analyses included in the fixed-sequence as described in Section 10.2 are listed below:

1. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT 1, 2, 3, 4, 5, and 6-infected subjects based on the PP population in the 8-week treatment duration achieving SVR_{12} is greater than 94%;
2. Efficacy of the 8-week treatment duration compared to the historical 12-week treatment duration will be demonstrated if the lower bound of the two-sided 95% confidence interval for the percentage of HCV GT 1, 2, 3, 4, 5, and 6-infected subjects based on the ITT population in the 8-week treatment duration achieving SVR_{12} is greater than 93%.

Only if success was demonstrated for both primary efficacy analyses will testing proceed to the two key secondary efficacy analyses in the order listed above. If success has been demonstrated for the first key secondary efficacy analysis of SVR_{12} based on the PP population in HCV GT 1 - 6-infected subjects, then testing will proceed to the second key secondary efficacy analysis of SVR_{12} based on the ITT population in HCV GT 1 - 6-infected subjects.

10.4.2 Other Secondary Efficacy Analyses

The other secondary efficacy analyses, which are not included in the fixed sequence, are listed below:

- The percentage of HCV GT3-infected subjects in the PP population who achieve SVR_{12};
- The percentage of HCV GT3-infected subjects in the ITT population who achieve SVR_{12};
- The percentage of subjects in the ITT population with on-treatment virologic failure (defined as **On-treatment virologic failure**), and
- The percentage of subjects in the ITT population with post-treatment relapse (defined as **$Relapse_{12}$**; subjects with reinfection will be summarized separately).

For the analyses of SVR_{12} among HCV GT3-infected subjects, the number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using Wilson's score method.

For the analysis of on-treatment virologic failure and post-treatment relapse, the number and percentage of subjects in the ITT population will be summarized along with a two-sided 95% confidence interval using Wilson's score method.

10.5 Sensitivity Analyses

The two-sided 95% confidence interval using Wilson's score method will also be calculated, if applicable, as a sensitivity analysis for the primary and key secondary efficacy analyses of SVR_{12} based on the PP and ITT populations.

The percentage of subjects in the mITT-GT and mITT-GT-VF populations achieving SVR_{12}, as applicable, will be summarized as well as the corresponding two-sided 95% confidence interval using Wilson score's method and the normal approximation to binomial distribution.

Listings of subjects excluded from the mITT-GT, mITT-GT-VF, and PP populations will be provided, as applicable.

10.5.1 Imputation Approaches

In addition to imputing SVR_{12} as described in Section 6.3, SVR_{12} will be presented in the ITT population using the following other methods to impute missing HCV RNA values:

- imputing any missing HCV RNA values in the SVR_{12} window by carrying forward the last non-missing (post-baseline) HCV RNA value prior to the SVR_{12} window.
- impute as described in Section 6.3 but treat SVR_{12} non-responders who were categorized as "prematurely discontinued study drug with no on-treatment virologic failure" or "missing follow-up data in the SVR_{12} window" as successes.

For each of these, the percentage of subjects with SVR_{12} will be presented along with two-sided 95% Normal and Wilson score confidence intervals.

10.6 Efficacy Subgroup Analysis

The subgroup analyses will be performed based on the ITT and mITT-GT-VF populations. The number and percentage of subjects with SVR_{12} will be presented for the following subgroups:

- HCV genotype and subtype (as defined in Section 10.8);
- Sex (male or female);
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Race (White, Black/African-American, Asian, or other) and (black or non-black);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Geographic region (North America, Europe, or ROW);
- Baseline BMI (< 30, or ≥ 30 kg/m^2);
- Baseline HCV RNA level (< 800,000 or ≥ 800,00 IU/mL; < 1,000,000 or ≥ 1,000,000 IU/mL);
- Baseline Child-Pugh score (5, 6, or > 6)
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L; < 150 or ≥ 150 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline FibroTest (< 0.75 or ≥ 0.75);
- Baseline APRI (≤ 1, > 1 to ≤ 2, or > 2);
- Baseline FIB-4 (< 1.45, ≥ 1.45 to ≤ 3.25, or > 3.25);
- Baseline AST/ALT ratio (≤ 1 or >1);
- Baseline total bilirubin (< 34.2 or ≥ 34.2 umol/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, or ≥ 90 mL/min);
- Baseline eGFR (< 60, ≥ 60 to < 90, or ≥ 90 mL/min/1.73 m^2);
- Subject on stable opiate substitution (yes/no);
- History of diabetes (yes/no);
- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no).

The 2-sided 95% confidence interval using Wilson's score method will be produced if there are at least 10 subjects in the subgroup.

In addition, stepwise logistic regression will be performed on SVR_{12} with all subgroup variables used as predictors of response based on the mITT-GT-VF population. Some

variables will be treated as continuous to decrease the chance of separation or quasi-separation and some variables may be eliminated if missing for many subjects.

10.7 Additional Efficacy Analyses

The following additional efficacy analyses will be performed in the ITT population:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects who achieve SVR_4 (HCV RNA < LLOQ 4 weeks after the last actual dose of study drug);
- The percentage of subjects who achieve SVR_{24} (HCV RNA < LLOQ 24 weeks after the last actual dose of study drug);
- The percentage of subjects who experience post-treatment relapse after achieving SVR_{12} (**$Relapse_{24}$**).

In the above analyses for SVR, virologic failure, and relapse, the percentage of subjects with a two-sided 95% Wilson score interval will be summarized. Imputations for missing data will be performed as described in Section 7.0 for analysis of SVR, where a missing response will be imputed as a failure after performing the described imputation. All other endpoints 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 SVR_4, SVR_{12}, SVR_{24} windows or after SVR_{24} window), including the subject number and the SVR visit window corresponding to the first occurrence of relapse. A similar listing 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.

The number and percentage of subjects who do not achieve SVR_{12} will be summarized by reason for non-response (as defined in Section 10.1). A listing of subject numbers and reason for non-response will be prepared. A similar summary and listing will be prepared for subjects who do not achieve SVR_{24}.

The concordance between SVR_{12} and SVR_{24} will be assessed by the agreement between SVR_{12} and SVR_{24} and the positive predictive value (PPV) and negative predictive value (NPV) of SVR_{12} on SVR_{24}. The agreement between SVR_{12} and SVR_{24} is a percentage defined as the number of subjects achieving both SVR_{12} and SVR_{24} and the number of subjects where both SVR_{12} and SVR_{24} are not achieved. The PPV of SVR_{12} on SVR_{24} is the proportion of subjects who achieve SVR_{12} and SVR_{24} out of all subjects who achieved SVR_{12}. The NPV of SVR_{12} on SVR_{24} is the proportion of subjects who neither achieve SVR_{12} nor SVR_{24} out of all subjects who did not achieve SVR_{12}. Similarly, the concordance between SVR_4 and SVR_{12} will be summarized.

10.8 Resistance Analyses

For all subjects, full length NS3/4A or 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 genes from the first sample after virologic failure with HCV RNA $\geq$ 1000 IU/mL will be sequenced by NGS. An appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples. Subjects who experience virologic failure (VF) will be referred to as subjects in the primary virologic failure (PVF) population, and a listing by subject that includes HCV genotype/subtype, IL28B genotype, reason for SVR_{12} non-response, time point(s) sequenced as closest to time of VF, and HCV RNA value at the VF time point(s) will be produced for these subjects. In addition, all listings described below will display HCV genotype/subtype and reason for SVR_{12} non-response in the subject identifier for each subject. A separate listing will summarize all subjects in the PVF population for whom no sequencing was performed (e.g., lost to follow-up while HCV RNA $\leq$ 1000 IU/mL).

Subjects treated with study drug who do not achieve SVR_{12} due to reasons other than virologic failure (prematurely discontinued study drug with no on-treatment virologic failure, HCV reinfection, missing SVR_{12} data, or other reasons as described in Section 10.1, Reasons for SVR_{12} 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. These subjects will be referred to as the non-PVF population. A listing of all subjects in the non-PVF population with post-baseline sequencing available will be created that is similar to the listing of subjects in the PVF population with post-baseline sequencing available.

Included time points for analyses on samples from subjects who do not achieve SVR_{12} 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 substitutions were detected by NGS at the time of HCV virologic failure/treatment discontinuation.

For each DAA target, signature amino acid positions and a key subset of amino acid positions are listed in Table 6. Appropriate subtype-specific prototypic reference sequence will be used for comparison with sequences from samples.

Table 6. 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	

The following definitions will be used in the resistance analyses:

- Baseline polymorphism: a polymorphism by NGS in a baseline sample (≥ 2% or ≥ 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 ≥ 2% of the sequences from the post-baseline sample.
- Enriched substitution: substitution 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 substitution.

Analysis 1: The following analyses will be provided for all subjects, separated by HCV subtype:

- A listing of all baseline polymorphisms (2% detection threshold) at signature amino acid positions for each DAA target (NS3/4A and NS5A) (ITT).
- A listing of all baseline polymorphisms (15% detection threshold) at non-signature amino acid positions for each DAA target (NS3/4A and NS5A) for subjects in the PVF population.
- 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% (ITT). This table includes prevalence of each baseline polymorphism, and a summary of number of subjects with polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A.
- 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) (ITT).
- 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 genotype, and total (include all genotypes) (ITT).

Analysis 2: The impact of baseline polymorphisms on treatment outcome will be assessed for the mITT-GT-VF population as follows: for each polymorphism, the SVR_{12} rate will be calculated for subjects with and without the polymorphism and the 2 rates will be compared. Analysis will be grouped by HCV subtype 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%.
- Polymorphism at each non-signature amino acid position (vs. no polymorphism at that 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 SVR_{12} rate will be calculated for the mITT-GT-VF population, and the rates with or without polymorphisms will be compared using Fisher's exact test. Analysis will be separated by HCV subtype. The following tables will be provided:

- Comparison of SVR_{12} rates by subtype, and total (include all subtypes)
- Comparison of SVR_{12} rates by genotype, and total (include all genotypes)

Analysis 4: The following analyses will be performed for subjects who do not achieve SVR_{12} 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 substitutions at signature amino acid position relative to the baseline amino acid sequence will be provided for each DAA target (NS3 and NS5A).
- The persistence of post-baseline variants at signature resistance-associated amino acid positions for each target (NS3 and NS5A) from subjects will be assessed at Post-Treatment Week 24. Listings by subject and time point of all treatment-emergent variants will be provided for each DAA target (NS3 and NS5A).

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 and resistance analyses.

A summary of HCV 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.

10.9 Patient Reported Outcomes

The following instruments will be used to collect patient reported outcomes (PROs): TSQM, SF-36v2[2] and FSS. Missing data for each measurement will be handled as described in Section 6.3.

The TSQM is a 14-item instrument and includes assessments of satisfaction with a medication's effectiveness (Effectiveness, three items), lack of side effects (Side Effects; five items), convenience (three items) and the subject's global satisfaction (Global Satisfaction; three items). No imputation will be applied to each measurement for missing items. TSQM scores range from 0 – 100 with higher scores indicating better satisfaction.

The SF-36v2 measures dimensions of a patient's functional health and well-being in 8 domains and also provides 2 summary scores that characterize a patient's mental (Mental Component Summary; SF-36-MCS) and physical (Physical Component Summary; SF-36-PCS) health status. Imputation will be applied to each domain as described in Section 6.3. The score for each of the 8 domains ranges from 0 to 100 and will be normalized according to the user manual. The standardization of the normalized scores will provide the norm-based scores with a mean of 50 and a SD of 10. The two summary scores are based on the norm-based scores. Per the SF-36v2 instrument manual, score for any item with multiple responses will be set to "missing." Subject's responses to the SF-36v2 will be summarized for the SF-36-PCS and SF-36-MCS measures and eight individual domain measures.

The FSS measures the impact of fatigue over the past week on specific types of functioning. The survey consists of 9 questions using a 7-point Likert scale. A total score

is calculated as the average of the individual item responses (adding up all the answers and dividing by nine). Higher FSS scores indicate a higher degree of impact of fatigue. Imputation will be applied to the total score as described in Section 6.3.

Summary statistics (n and mean) at each visit and for the change from baseline (n, mean, SD, minimum and maximum) to each applicable post-baseline timepoint will be provided for SF-36v2 (SF-36-PCS and SF-36-MCS and eight individual domains) scores and for the FSS total score. In addition, summary statistics (n, mean, SD, median, minimum and maximum) for the TSQM subscales (global satisfaction, convenience, effectiveness, side effects) at Weeks 2, 4, and 8 will be provided.

The following analyses of PROs also will be performed:

- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 3 points in the SF-36-MCS and SF-36-PCS;
- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 5 points in the SF-36-MCS and SF-36-PCS;
- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 5 points in the SF-36 domain scores;
- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 0.7 in the FSS total score;
- Number and percentage of subjects who have experienced an increase from baseline at each applicable timepoint of greater than or equal to 1 in the FSS total score.

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 data will be summarized using the safety population.

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 SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

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 (GLE/PIB);
- Treatment-emergent AEs of grade 3 or higher;
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (GLE/PIB);
- Treatment-emergent AEs leading to discontinuation of study drug;
- DAA-related treatment-emergent AEs leading to discontinuation of study drug;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to DAAs (GLE/PIB);
- 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 Event by SOC and PT

Subjects reporting more than one AE for a given preferred term 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 an SOC will be counted only once for that SOC. Subjects reporting more than one AE will be counted only once in the overall total.

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

- Treatment-emergent AEs;
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (GLE/PIB);
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (GLE/PIB);

- Grade 3 or higher treatment-emergent AEs;
- Treatment-emergent AEs leading to discontinuation of study drug;
- DAA-related treatment-emergent AEs leading to discontinuation of study drug;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to DAAs (GLE/PIB);
- 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 adverse events grouped by body system and preferred term with subject numbers will be created.

Adverse Event by PT

The number and percentage of subjects experiencing treatment-emergent AEs will be tabulated according to PT and sorted by overall frequency. 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 PT. 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 Event by Maximum Relationship

Treatment-emergent AEs also will be summarized by maximum relationship of each PT 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.

Adverse Events of Special Interest

For the hepatic decompensation/hepatic failure AE of special interest defined below, the number and percentage of subjects experiencing at least one treatment-emergent AE in the search will be presented overall and by SOC and PT. In addition, a listing of treatment-emergent AEs for subjects meeting the search criterion will be provided. For the hepatocellular carcinoma AE of special interest, a listing of all AEs meeting the search criterion will be provided.

- Hepatic decompensation and hepatic failure
  - Treatment-emergent events only
  - Product MedDRA Query (PMQ) of "Hepatic decompensation and hepatic failure"
- Hepatocellular carcinoma
  - All post-baseline cases, treatment-emergent and non-treatment emergent
  - Search based on specific MedDRA preferred terms of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent.

11.2.3 Listing of Adverse Event

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.

11.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional lab testing due to an SAE, will be used in all analyses. The protocol-defined hematology and clinical chemistry laboratory tests will be summarized.

Some of the laboratory variables are calculated by the laboratory vendor including indirect bilirubin, creatinine clearance, and eGFR by MDRD. The central lab calculates eGFR by MDRD using the following equation, where serum creatinine is measured in mg/dL and age is measured in years:

$$\text{GFR (mL/min/1.73 m}^2) = 175 \times (\text{Serum Creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times 1.212 \text{ (if Black)} \times 0.742 \text{ (if Female).}$$

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

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

11.3.1 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 change to Treatment Period visits and change to PT Period visits.

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

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 the normal ranges of the laboratory used for each sample. A shift table from baseline to minimum value and maximum value during the Treatment Period will be created. In this shift table, the number and percentage of subjects with baseline values within or above the normal range (baseline high or normal) and a minimum value below the normal range (post-baseline low) and the number and percentage of subjects with baseline values within or below the normal range (baseline low or normal) and a maximum value above the normal range (post-baseline high) will be summarized.

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. 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.

The laboratory parameters defined in Table 7 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 summarized. The post-baseline value must be in a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value in order to be counted. The summary will also include the number and percentage of subjects with a maximum of

at least Grade 3 for all laboratory parameters in Table 7. A listing of all relevant laboratory parameters will be provided for each subject who had an increase to Grade 2 or higher for all laboratory variables in Table 7.

Table 7. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT/SGPT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
AST/SGOT	> 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	--

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 × ULN (regardless of grade change);
- Total bilirubin ≥ 2 × ULN and > baseline (i.e., a post-baseline value must be more extreme than the baseline value to be considered);
- Post-nadir ALT > 3 × ULN and total bilirubin > 2 × ULN;
- Post-nadir ALT > 3 × ULN and total bilirubin ≤ 2 × 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 × ULN;
- Post nadir ALT > 3 × ULN and a concurrent total bilirubin > 2 × 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 × ULN;
- Post-nadir ALT > 3 × ULN and total bilirubin > 2 × 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 × 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 × ULN followed by lost to follow-up (no additional ALT values) also will be considered as confirmed (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 8.

Table 8. 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 ≥ 15% from baseline	An increase of ≥ 15% from baseline
Body Temperature		> 38.3°C AND An increase of ≥ 1.1°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 change to TP visits and change to PT Period visits.

Mean changes from baseline to each post-baseline visit, including applicable PT visits, will be summarized. Each vital sign parameter will be summarized with the baseline mean, visit mean, 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 8) 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.

12.0 Summary of Changes

12.1 Summary of Changes from SAP Version 1.0

- Updates were made to the study objectives, sample size, and efficacy analysis sections to reflect the changes in protocol Amendment 3 regarding the inclusion of GT3 subjects.
- The list of variables to be used in the summary of demographic and baseline characteristics as well as the subgroup analysis were slightly modified to be consistent with protocol Amendment 3 (e.g., adding in genotype 3 and subtypes, and geographic region).
- The language in the section on the analysis of hepatic laboratory abnormalities of interest was edited to be consistent with analysis plans across the GLE/PIB Phase 3b program.

13.0 References

1. Julious SA. Two-sided confidence intervals for the single proportion: comparison of seven methods by Robert G. Newcombe, Statistics in Medicine 1998;17:857-872. Stat Med. 2005;24(21):3383-4.
2. Ware JE Jr, Kosinski M, Bjorner JB, et al. User's manual for the SF-36v2 health survey. 2nd ed. Lincoln, RI: QualityMetric Incorporated; 2007.