1.0 Title Page

Statistical Analysis Plan

Study M16-126

A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Adults with Chronic Hepatitis C Virus (HCV) Genotype 5 or 6 Infection

Date: 15 May 2018

Version 1.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the AbbVie Statistics and Statistical Programming Departments for glecaprevir (GLE)/pibrentasvir (PIB) study Protocol M16-126. Study M16-126 evaluates the efficacy and safety of GLE/PIB in HCV treatment-naïve or treatment-experienced (i.e., has failed prior interferon [IFN] or pegylated-IFN [pegIFN] with or without ribavirin [RBV], or sofosbuvir [SOF] plus RBV with or without pegIFN therapy), chronic hepatitis C virus (HCV) genotype (GT) 5 or 6-infected subjects, without cirrhosis for an 8-week treatment duration or with compensated cirrhosis for a 12-week treatment duration.

This SAP (Version 1.0) provides details to further elaborate the statistical methods outlined in Clinical Study Protocol M16-126 incorporating Amendment 1 dated 28 July 2017, and describes analysis conventions to guide the statistical programming. Unless noted otherwise, all analyses will be performed using SAS® Version 9.4 (SAS Institute Inc., Carry, NC 27513) or later under the Unix operating system.

The SAP will not be updated in the case of future administrative or minor amendments to the protocol unless the changes have any impact on the analysis of study data.

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 a 12-week sustained virologic response, SVR_{12}) and safety of GLE/PIB in adults with chronic HCV GT5 or 6 infection with or without compensated cirrhosis.

The secondary objectives are to assess the efficacy of GLE/PIB in adults with HCV GT 5 or 6 infection with or without compensated cirrhosis by evaluating the percentages of subjects with on-treatment virologic failure and post-treatment relapse.

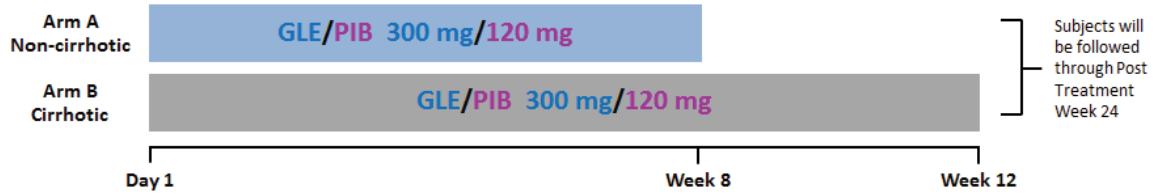
4.2 Design Diagram

Study M16-126 is a Phase 3b, open-label, nonrandomized, multicenter study to evaluate the efficacy and safety of GLE/PIB in adults with chronic HCV GT5 or 6 infection, without cirrhosis or with compensated cirrhosis, who are either treatment-naïve or treatment-experienced with IFN or pegIFN with or without RBV or treatment-experienced with SOF plus RBV with or without pegIFN.

The study will enroll approximately 80 eligible subjects. A minimum of 15 GT5 and 30 GT6 subjects and up to approximately 16 subjects with compensated cirrhosis (regardless of GT) will be enrolled. Each subject will be assigned to one of two treatment arms based on their cirrhosis status. Non-cirrhotic subjects (Arm A) will be treated with GLE/PIB 300 mg/120 mg once daily for 8 weeks, while subjects with compensated cirrhosis (Arm B) will be treated with GLE/PIB 300 mg/120 mg once daily for 12 weeks.

Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 1, 2, 4, and 8 for all subjects and an additional Week 12 visit for subjects in Arm B. Subjects who complete or prematurely discontinue study drug will be followed for 24 weeks. During the Post-Treatment Period, all subjects will have visits at Post-Treatment Weeks 4, 12, and 24.

Figure 1. Study Schematic



4.3 Sample Size

In Phase 2 and 3 studies, Study M14-868 and Study M14-172, GT 5 and 6 subjects were enrolled to demonstrate the pangenotypic efficacy of GLE/PIB across GT1-6 for the label

approved treatment duration. The current study, Study M16-126, serves to generate additional efficacy and safety data from GT 5 and 6 subjects in a wider geographic region. Therefore, no formal hypothesis will be tested in this study. The sample size of this study is determined based on operational considerations of enrolling subjects with less common HCV genotypes.

If the observed SVR_{12} rate in this study is 97% among the expected 30 GT5 and 50 GT6 subjects, then the expected 95% confidence intervals (CIs) for the SVR_{12} rate using the Wilson's score method[1] are (84.2%, 99.3%) and (88.2%, 99.1%), respectively, based on the Wilson's score CIs calculated for 1000 simulated samples of 30 GT5 and 50 GT6 subjects with an SVR_{12} rate of 97% using SAS®. The Wilson's score method is expected to be used instead of the normal approximation method because the number of SVR_{12} non-responders is expected to be less than 5 (see Section 10.3).

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. Results from the primary analysis (e.g., SVR_{12} data) will be described in the primary clinical study report (CSR).

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 and included in the final CSR (results related to SVR_{12} will not be updated).

There is no intention of stopping the study early based on efficacy findings from 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 for Analysis Populations

5.1.1 Intention-to-Treat (ITT) Population

All enrolled subjects who receive at least one dose of study drug will be included in the ITT population. Demographic, baseline characteristics, exposure, compliance, concomitant medication and medical history analyses will be performed on the ITT population overall and according to the treatment arm assignment, i.e., subject grouping will be based on the arm to which the subject was assigned. Demographic and baseline characteristics will also be summarized by GT. Efficacy analyses will be performed by GT (GT5 and GT6) and for the overall ITT population.

5.1.2 Modified Intention-to-Treat (mITT) Populations

Sensitivity analyses of SVR_{12} as described in Section 10.5, when applicable, will be performed on the ITT population modified to exclude subjects who do not have HCV GT5 or 6 infection or with multiple/mixed genotypes (final HCV genotype as determined in Section 10.8) (mITT-GT), and on the mITT-GT population further modified to exclude subjects who do not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-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 analyses will be performed on the overall safety population, combining Arms A and B.

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 collected 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 both 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 and resistance, the time windows specified in Table 1 and Table 2 describe how these 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, patient reported outcome (PRO) data 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 for when used 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., SVR_{12}), 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, Resistance Endpoints, Safety 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	≤ 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. For Arm B only.

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. 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 Visit and End of Treatment Visit (Week 8 for Arm A and Week 12 for Arm B, 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 to 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}. 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, Vital Sign Measurements, and PRO Instruments (Post-Treatment Period)

Scheduled Time[a]	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[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 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, urinalysis, and coagulation panels are collected at Post-Treatment Week 4 Visit or at Post-Treatment Discontinuation Visit if subject discontinues prior to Post-Treatment Week 4. PRO instruments are collected at Post-Treatment Week 12 Visit.

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 PROs will be as follows. If a respondent answers at least 50% of the items in a multi-item scale of the Short Form 36 Version 2 (SF-36v2) Health Status Survey, 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. Missing data handling conventions for scores related to the Work Productivity and Activity Impairment Questionnaire (WPAI) – Hepatitis C are specified in Section 10.9.

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

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

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 variables include age, weight, height, waist circumference, and body mass index (BMI). Categorical demographic variables include sex, race, Asian race (Asian or non-Asian), types of Asian race (as captured in the eCRF form 'Demographics': Japanese, Chinese, Korean, Taiwanese, and Other, which can include Vietnamese, Burmese, Cambodian, etc.), 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, Asia, or rest of world [ROW]).

When defining geographic region, sites in the United States and Canada will be grouped under North America; sites in Belgium and France will be grouped under Europe; sites in

Singapore and Vietnam will be grouped under Asia; sites in Australia, New Zealand and South Africa will be grouped as ROW.

Continuous baseline characteristics include baseline $\log_{10}$ HCV RNA level, homeostasis model of assessment – insulin resistance (HOMA-IR), creatinine clearance (Cockcroft-Gault calculation), eGFR (using the modification of diet in renal disease [MDRD] formula), platelet count, albumin, GGT, LDL, HDL, APRI, FIB-4, AST, ALT, total, direct, and indirect bilirubin.

Categorical baseline characteristics include:

- HCV GT (5, or 6) and available subtype (as determined by the central laboratory);
- Cirrhosis status (cirrhotic or non-cirrhotic);
- Prior HCV treatment history (naïve or experienced);
- For treatment-experienced subjects, type of previous regimen (IFN- or SOF-based);
- For treatment-experienced subjects, type of non-response to previous treatment (on-treatment non-responder, breakthrough, post-treatment relapse, or unknown/other);
- IL28B genotype (CC, CT, or TT; CC or non-CC);
- Baseline HCV RNA level (< 1,000,000 or ≥ 1,000,000 IU/mL, < 2,000,000 or ≥ 2,000,000 IU/mL);
- Baseline fibrosis stage (equivalent to Metavir F0 - F1, F2, F3, or F4);
- Baseline platelet count (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, ≥ 90 mL/min);
- Baseline eGFR (< 90, ≥ 90 mL/min/1.73 m^2);
- History of diabetes (yes/no);
- History of bleeding disorders (yes/no);
- History of depression or bipolar disorder (yes/no);

- History of cardiovascular disease (yes/no);
- Baseline metabolic syndrome (yes/no);
- Injection drug use (yes, within last 12 months; yes, more than 12 months ago; or no);
- Use of stable opiate substitution (yes/no);
- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no);
- Tobacco use (current, former, never, or unknown);
- Alcohol use (current, former, never, or unknown).

In addition, for cirrhotic subjects, the following will be summarized:

- Baseline Child-Pugh score (5, 6, or > 6).

Summaries of baseline resistance are described in Section 10.8.

For treatment-experienced 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.

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

HOMA-IR is defined as fasting glucose (mmol/L) × fasting insulin (μIU/mL) ÷ 22.5. Subjects who do not have concurrent fasting glucose and fasting insulin values at baseline will be excluded from the summary of baseline HOMA-IR.

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 4.

Presence or absence of cirrhosis will be determined as collected in EDC ("What is the subject's cirrhosis status?" – "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 5.

Baseline APRI and FIB-4 are defined as 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.

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

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

Table 4. 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.

Table 5. 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 to medication)

* 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.

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:

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

Subjects will be classified as having metabolic syndrome if at least 3 of the 5 characteristics in Table 6 are present.

Table 6. Clinical Identification of Metabolic Syndrome

Risk Factor	Defining Level in Conventional Units	Defining Level in SI Units
Abdominal obesity, given as waist circumference		
Men	> 40 in	> 102 cm
Women	> 35 in	> 88 cm
Triglycerides	≥ 150 mg/dL	≥ 1.695 mmol/L
HDL cholesterol		
Men	< 40 mg/dL	< 1.03452 mmol/L
Women	< 50 mg/dL	< 1.29315 mmol/L
Blood pressure (BP)	Systolic BP ≥ 130 or Diastolic BP ≥ 85 mmHg	Systolic BP ≥ 130 or Diastolic BP ≥ 85 mmHg
Fasting glucose	≥ 100 mg/dL	≥ 5.5507 mmol/L

Reference: Grundy 2004.[2]

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

Table 7. Medical History eCRF

	Medical 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

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. 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 summaries of all prior and concomitant medications.

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 by investigator for each treatment arm and overall.

- 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 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 and overall. 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

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 duration of exposure during the Treatment Period.

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

- > 90 days

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

9.2 Compliance

At each visit (starting with the Week 4 visit) during the Treatment Period, the total number of tablets dispensed and returned for each kit is recorded. The compliance for the 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. If a subject is not able to return any of the dispensed kit, that subject's compliance will be regarded as missing.

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 for each treatment arm and overall. A listing of compliance for each subject will be provided. The percentage of compliant subjects will be summarized for each treatment arm and overall, based on data as observed. Subjects with missing values for compliance will not be included in the denominator.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

All efficacy analyses will be performed on the ITT population, unless otherwise specified. To support the primary analysis, sensitivity analyses will be conducted for it using the mITT-GT and mITT-GT-VF populations.

Missing data will be imputed for analyses of the HCV RNA endpoints of SVR and virologic failure as described in Section 6.3 and for analyses of PROs as described in Section 6.3 and Section 10.9.

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 ≥ 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 ≥ 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; if a subject meets both definitions of Breakthrough and EOT failure, he or she will be categorized as Breakthrough only.

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} window) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment, excluding reinfection as described below.

$Relapse_{24}$ = confirmed HCV RNA ≥ LLOQ within the SVR_{24} window for a subject who achieved SVR_{12} and has HCV RNA data available in the SVR_{24} window, excluding reinfection.

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

Virologic failure for SVR_{12} = On-treatment virologic failure or **$Relapse_{12}$**.

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 any subject with study drug duration of 52 days or greater for Arm A, and 77 days or greater for Arm B. 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 NS3/4A 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 NS3/4A or NS5A, and/or NS5B 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 subgenotype 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);

2. HCV reinfection (see definition described earlier);
3. $Relapse_{12}$;
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 in Arm A, and < 77 days for subjects in Arm B] and did not meet the **On-treatment virologic failure or HCV reinfection** definitions);
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);
2. HCV reinfection;
3. $Relapse_{12}$;
4. $Relapse_{24}$;
5. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{24} non-responder who prematurely discontinued study drug [study drug duration < 52 days for subjects in Arm A, and < 77 days for subjects in Arm B] and did not meet the **On-treatment virologic failure**, **HCV reinfection**, **$Relapse_{12}$**, 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} and SVR_{24} nonresponse defined above, subjects are only to be counted in one category in the order shown above. Specifically, subjects who were SVR_{12} or SVR_{24} 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, $Relapse_{12}$ or $Relapse_{24}$.

10.2 Handling of Multiplicity

No multiplicity adjustment is needed for this study because there is no hypothesis testing for the primary and secondary efficacy endpoints.

10.3 Primary Efficacy Analysis

The primary efficacy endpoint is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in the ITT population. The number and percentage of subjects achieving SVR_{12} will be summarized by GT (GT5 and GT6) across treatment arms. The number and percentage of subjects achieving SVR_{12} will be calculated along with a two-sided 95% CI using the normal approximation to the binomial distribution, unless the number of SVR_{12} non-responders is less than 5, where the Wilson's score method[1] will be used to calculate the CI instead.

A summary of reasons for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, other) will be provided. A listing of subjects who do not achieve SVR_{12} by reason for non-response will also be provided.

10.4 Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment virologic failure;
- The percentage of subjects with $Relapse_{12}$.

The number and percentage of subjects with on-treatment virologic failure and $Relapse_{12}$ in the ITT population will be summarized along with two-sided 95% Wilson score CIs by GT (GT5 and GT6) across treatment arms.

10.5 Sensitivity Analyses for SVR

As sensitivity analyses, the number and percentage of subjects in the mITT-GT and mITT-GT-VF populations achieving SVR_{12} will be summarized by GT (GT5 and GT6) across treatment arms, along with two-sided 95% CIs using the normal approximation to the binomial distribution and the Wilson's score method.

A different CI will be calculated for the primary endpoint of SVR_{12} based on the ITT population as a sensitivity analysis. If the number of SVR_{12} non-responders is ≥ 5, then the two-sided 95% CI using Wilson's score method will be calculated. If the number of SVR_{12} non-responders is < 5, the two-sided 95% CI using the normal approximation to the binomial distribution will be calculated.

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

10.6 Efficacy Subgroup Analysis

The percentage of subjects with SVR_{12} in the ITT population will be presented along with two-sided 95% Wilson score CIs by GT (GT5 and GT6) across treatment arms, and overall, for the following subgroups:

- Prior HCV treatment history (naïve or experienced);

- For treatment-experienced subjects, type of previous regimen (IFN- or SOF-based);
- IL28B genotype (CC or non-CC);
- Sex (male or female);
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Race (White, Black/African-American, Asian, or other) and (Asian or non-Asian);
- Baseline BMI (< 30 or ≥ 30 kg/m^2);
- Baseline HCV RNA level (< 1,000,000 or ≥ 1,000,000 IU/mL, < 2,000,000 or ≥ 2,000,000 IU/mL);
- Baseline fibrosis stage (F0 – F1, F2, F3, or F4);
- Baseline cirrhosis status (yes/no);
- Baseline platelet count (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, ≥ 90 mL/min);
- Baseline eGFR (< 90 or ≥ 90 mL/min/1.73 m^2);
- History of diabetes (yes/no);
- Baseline metabolic syndrome (yes/no);
- Use of stable opiate substitution (yes/no);
- Former injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no)

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

10.7 Additional Efficacy Analyses

As additional analyses, the analyses of SVR_{12} (as described in Section 10.3) and on-treatment virologic failure and $Relapse_{12}$ (as described in Section 10.4) in the ITT population and the sensitivity analyses of SVR_{12} in the mITT-GT and mITT-GT-VF populations (as described in Section 10.5) will be performed for the overall population

across treatment arms and genotypes. For the SVR_{12} endpoints, two-sided 95% CIs using both the normal approximation to the binomial distribution and the Wilson's score method will be calculated. For the other endpoints, only the two-sided 95% CI using Wilson's score method will be calculated.

The following additional efficacy endpoints will be summarized and analyzed for the ITT population, by GT (GT5 and GT6) across treatment arms and overall:

- 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 with SVR_4;
- The percentage of subjects with SVR_{24};
- The percentage of subjects who relapsed after achieving SVR_{12} (**$Relapse_{24}$**).
- 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 **$Relapse_{12}$**)

For each of the above endpoints, a two-sided 95% CI using Wilson's score method will be calculated along with the number and percentage of subjects. Imputations for missing data will be performed as described in Section 6.3 for all the additional endpoints listed above except the first one.

For the overall ITT population and by GT, a summary of the subjects who completed treatment and relapsed (defined as **$Relapse_{overall}$**) will be prepared displaying the number and percentage of subjects relapsing overall and by the SVR visit window where the first relapse occurred (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 summary will be prepared for subjects who prematurely discontinued treatment and relapsed after having HCV RNA < LLOQ at their Final Treatment Visit.

The number and percentage of subjects who do not achieve SVR_{24} will be summarized by reason for non-response (as defined in Section 10.1) for the overall ITT population and by GT. For the overall ITT population, the number and percentage of subjects who do not achieve SVR_{12} will also be summarized by reason for non-response. Listings of the subject numbers of those who do not achieve SVR_{12} and SVR_{24} and the reasons for non-response will also be prepared.

The concordance between SVR_{12} and SVR_{24} will be assessed for the overall population (across genotype and treatment arm) 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_{24} out of all subjects who achieved SVR_{12}. The NPV of SVR_{12} on SVR_{24} is the proportion of subjects who do not achieve SVR_{24} out of all subjects who did not achieve SVR_{12}. Similarly, the concordance between SVR_4 and SVR_{12} will be summarized for the overall population.

10.8 Resistance Analyses

For all subjects, full length NS3/4A and NS5A will be sequenced from baseline samples by next generation sequencing (NGS). For all subjects who experience virologic failure (on-treatment virologic failure or $Relapse_{overall}$ as defined in Section 10.1), full length NS3/4A and NS5A genes from the first sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. For all other subjects who do not achieve SVR_{12} or SVR_{24} (prematurely discontinued study drug with no on-treatment virologic failure, HCV reinfection, missing SVR_{12} or SVR_{24} data or other reasons as described in Section 10.1, **Reasons for SVR_{12} Non-Response** and **Reasons for SVR_{24} Non-Response**) but have a post-treatment time point with HCV RNA ≥ 1000 IU/mL, full length NS3/4A and NS5A genes from the first post-treatment sample with HCV RNA ≥ 1000 IU/mL will also be sequenced by NGS.

For all subjects who do not achieve SVR_{12} or SVR_{24}, a listing by subject that includes HCV genotype/subtype, reason for SVR_{12} or SVR_{24} non-response, and baseline resistance data availability besides key baseline characteristics will be produced.

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

Table 8. Signature Amino Acid Positions and Key Subsets of Amino Acid Positions

Target/Genotype	Signature Amino Acid Positions	Key Subset of Amino Acid Positions
NS3		
5, 6	36, 43, 54, 55, 56, 80, 155, 156, 168	155, 156, 168
NS5A		
5, 6	24, 28, 29, 30, 31, 32, 58, 92, 93	24, 28, 30, 31, 58, 92, 93

Included time points for analyses on available samples from subjects who do not achieve SVR_{12} are: 1) the sample closest in time after HCV virologic failure/treatment 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 (≥ 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 or NS5A).
- Variant at signature amino acid position: variant (relative to reference) present in a baseline or a 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 variant: a variant 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 by NGS: a post-baseline substitution or an enriched variant.

Analysis 1

The following analyses will be performed for all subjects, separated by HCV genotype/subtype (including total):

- A listing of all subjects with baseline polymorphisms (2% detection threshold) at signature amino acid positions for each DAA target (NS3and NS5A) in the ITT population. HCV genotype/subtype and treatment outcome (SVR_{12} or reason for SVR_{12} non-response) will be displayed for each subject.
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15% for subjects in the ITT population. This table includes prevalence of each baseline polymorphism, and a summary of the number of subjects with polymorphisms in NS3 only, NS5A only, any in NS3 or NS5A, and in both NS3 and NS5A.
- Total number and percentage of subjects in the ITT population with baseline polymorphisms ***at a key subset of amino acid positions*** in NS3 only, in NS5A only, in NS3 + NS5A, any in NS3, any in NS5A, and any in NS3 or NS5A at 15% detection threshold.

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 two rates will be

compared using Fisher's exact test. Analysis will be grouped by HCV genotype/subtype (including total) and DAA target (NS3 or NS5A). The analysis will include the number of subjects within each genotype/subtype (including total) with polymorphisms in NS3 only, in NS5A only, any in NS3 or NS5A, and in both NS3 + 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%.

Analysis 3

In subjects with or without baseline polymorphisms in NS3 only, in NS5A only, in NS3 + NS5A, any in NS3, any in NS5A, and any in NS3 or NS5 ***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 genotype/subtype (including total).

Analysis 4

The following listings will be produced for subjects who do not achieve SVR_{12} or SVR_{24} and have post-baseline sequence available. HCV genotype/subtype and reason for SVR_{12} or SVR_{24} non-response will be displayed for each subject.

- Listings by subject and time point of all *treatment-emergent substitutions* relative to the baseline amino acid sequences will be provided for each DAA target (NS3 and NS5A).
- Listings by subject and time point of all *variants at signature amino acid positions* in a post-baseline time point relative to the appropriate prototypic

reference amino acid sequence will be provided for each DAA target (NS3 and NS5A).

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV sequence from baseline samples for all subjects in order to accurately determine their genotype/subtype.

Subjects' HCV genotype and subtype may be assessed based on the Inno-LiPA 2.0 Assay used by the Central lab (Covance), the HCV genotype determination by Sanger sequencing a region of NS5B by the Central lab (Covance) and/or from phylogenetic analysis of the full length NS3/4A, and/or NS5A sequences performed by AbbVie. If the phylogenetic analysis is available, then it will be used to determine the subject's HCV genotype and subtype. If it is not available, then the Sanger sequencing assay result will be used to determine the subject's HCV genotype and subtype, if available. Finally, if neither the phylogenetic analysis results nor the Sanger sequencing assay results are available, then the Inno-LIPA assay results will be used to categorize the subject.

This subtype 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 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 PROs: Short Form 36 - Version 2 (SF-36v2), Work Productivity and Activity Impairment-Hepatitis C (WPAI-HCV) Specific Instrument Version 2.

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; MCS) and physical (Physical Component Summary; 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.[3] The standardization of the normalized scores will provide the norm-based scores with a mean of 50 and a standard deviation of 10. The two summary scores are based on the norm-based scores. Per the SF-36v2 instrument manual, the score for any item with multiple responses will be set to "missing." Subjects' responses to the SF-36v2 will be summarized for the PCS and MCS measures and 8 individual domain measures.

The WPAI Hepatitis C consists of 6 questions: Q1 = currently employed; Q2 = hours missed due to HCV-related health problems; Q3 = hours missed other reasons; Q4 = hours actually worked; Q5 = degree hepatitis C affected productivity while working (using a 0 to 10 VAS); Q6 = degree hepatitis C affected productivity in regular unpaid activities (VAS).

The four main impairment scores (S1 – S4) are expressed as percent impairment based on the above questions:

S1. Absenteeism (percent work time missed due to hepatitis C):

$$100 \times \left[\frac{Q2}{Q2 + Q4} \right]$$

S2. Presenteeism (percent impairment while working due to hepatitis C):

$$100 \times \left[\frac{Q5}{10} \right]$$

S3. Percent overall work impairment due to hepatitis C:

$$100 \times \left[\frac{Q2}{Q2+Q4} + \left\{ 1 - \frac{Q2}{Q2+Q4} \right\} \times \frac{Q5}{10} \right]$$

S4. Percent activity impairment due to hepatitis C:

$$100 \times \left[\frac{Q6}{10} \right]$$

The following missing data handling conventions are applied:

- Define Employment as a binary YES or NO variable where YES corresponds to "Employed" and NO corresponds to "Not Employed."
  - A subject will be considered "employed" at a given visit if Q1 = YES or Q2 > 0 or Q4 > 0.
  - A subject will be considered "unemployed" at a given visit if Q1 = NO and no positive hours recorded under Q2 and Q4 (i.e., if Q1 = NO AND Q2 ≤ 0 AND Q4 ≤ 0, then UNEMPLOYED).
  - Employment status for a subject will be considered "missing" at a given visit if Q1 = missing and no positive hours recorded under Q2 and Q4.
- If a subject is "unemployed" or employment status is "missing," then S1, S2, and S3 will be set to "missing."
- If Q2 = 0 and Q4 = 0 or missing then Q2/(Q2 + Q4) = missing (i.e., S1 = missing).
- If Q2 = 0 and Q4 = 0, then set S3 to missing.
- If Q2 is missing or Q4 is missing, then set S1 and S3 to missing.
- If Q4 = missing, then DO NOT set Q5 = missing.
- If Q5 is missing, then apply the following rules:
  - If Q2 > 0, Q4 = 0, and Q5 = missing, then S3 = 100%.
  - If Q2 = 0, Q4 > 0, and Q5 = missing, then S3 is missing.
  - If Q2 > 0, Q4 > 0, and Q5 = missing, then S3 is missing.

Summary statistics for each protocol-specified visit (number of non-missing observations and mean) and for change from baseline to each protocol-specified visit (number of non-missing observations, mean, standard deviation, minimum and maximum) will be provided for (1) the SF-36v2 PCS score, MCS score, and 8 individual domain scores, and (2) the WPAI-HCV activity impairment, overall work impairment, absenteeism, and presenteeism scores.

The following analyses of PROs also will be performed:

- Number and percentage of subjects who have experienced an increase from baseline at each applicable time point of greater than or equal to 2.5 points in the SF-36 MCS and PCS;
- Number and percentage of subjects who have experienced an increase from baseline at each applicable time point of greater than or equal to 5 points in the SF-36 domain scores;

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. Data will be summarized for the overall population across genotype and across treatment arm.

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

For all the summaries in this section, the number and percentage of subjects with treatment-emergent AEs will be tabulated.

Adverse Event Overview

An overview of AEs will be presented that consists of the number and percentage of subjects experiencing at least one event for each of the following treatment-emergent 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 Events by System Organ Class and Preferred Term

The number and percentage of subjects with treatment-emergent AEs will also be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) for the summaries listed below. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

- Treatment-emergent AEs;
- 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 leading to death.

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 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.

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.

A listing of treatment-emergent AEs grouped by SOC and PT with subject numbers will be created for each treatment arm.

Adverse Events by Preferred Term

The following summaries of treatment-emergent AEs tabulated according to PT and sorted by the overall frequency across the two treatment arms will be generated:

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

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 will be counted only once in the overall total.

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 tabulated by SOC. 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.

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 PTs 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 PT and across all SOCs/PTs. 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 Listing 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 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, cholesterol, total protein, glucose, triglycerides, albumin, chloride, bicarbonate, magnesium, total insulin, gamma-glutamyl transferase (GGT), creatinine clearance (calculated using Cockcroft-Gault formula), and eGFR (calculated using MDRD equation).

Urinalysis variables to be summarized include: specific gravity and pH.

The definitions of toxicity grades for laboratory parameters are presented in Table 9.

Table 9. 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
GGT	> 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	--
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
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	--
Glucose (increased)	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L	> 27.8 mmol/L
Glucose (decreased)	< 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
Creatinine clearance	< LLN – 60 mL/min	< 60 – 30 mL/min	< 30 – 15 mL/min	< 15 mL/min
Cholesterol	> ULN – 7.75 mmol/L	> 7.75 – 10.34 mmol/L	> 10.34 – 12.92 mmol/L	> 12.92 mmol/L
Albumin	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/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 to Treatment Period visits and changes to Post-Treatment Period visits.

Visit Values

For each laboratory parameter listed in Section 11.3.1, values at each visit (baseline and post-baseline, including applicable post-treatment visits) will be summarized with the

sample size, mean, standard deviation, minimum, median, and maximum. Figures presenting mean values over time will be produced.

Change from Baseline

For each laboratory parameter listed in Section 11.3.1, changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized with the sample size, baseline mean; visit mean; and change from baseline mean, standard deviation, minimum, median, and maximum.

Shift Tables

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.

Maximum Toxicity Grade

The laboratory parameters listed in Table 9 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 during the Treatment Period 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 9, 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 9.

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 hepatic laboratory values 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/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 hepatic laboratory values 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 (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 10.

Table 10. 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 changes to Treatment Period visits and changes to Post-Treatment Period visits.

For each vital sign parameter listed in Section 11.4.1, values at each visit (baseline and post-baseline, including applicable post-treatment visits) will be summarized with the sample size, 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 10) 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 Between the Latest Version of the Protocol and SAP Version 1.0

1. New expected confidence intervals are calculated in Section 4.3 **Sample Size** because the rule of choosing between the normal approximation method and

Wilson's score method for the primary endpoint has been updated in the protocol (also see Section 10.3)

2. All safety analyses have been changed to be performed only for the overall population because integrated safety analyses on Phase 3 studies showed no difference in safety profiles between subjects with compensated cirrhosis and without cirrhosis.
3. The race category of Black/non-Black has been changed to Asian/non-Asian in Section 7.1 and Section 10.6 because the Asian population is of interest to this study while very few Black subjects are expected to enroll. Also, different Asian types will be summarized among the baseline characteristics (Section 7.1).
4. The category of baseline HCV RNA level has been changed from 6,000,000 IU/mL to 2,000,000 IU/mL because it is a better cutoff based on previous studies.
5. Efficacy endpoints will also be summarized for the overall population (Section 10.6, Section 10.7 and Section 10.9) in order to provide results across all subjects in the study.
6. The integrated efficacy analysis combining GT5 and GT6 subjects from Studies M14-868 Part 4, M14-172 and M16-126 using meta-analytic methods has been removed because there is no plan for a label update with such data.
7. The resistance analyses (Section 10.8) have been updated to reflect current HCV project standards.
8. Text in PRO analyses of mean change from baseline has been updated for better clarity (Section 10.9).
9. Missing data handling conventions for scores related to the Work Productivity and Activity Impairment Questionnaire (WPAI) – Hepatitis C are specified in Section 10.9.
10. Methods for the assessment of hepatic laboratory values and hepatic laboratory abnormalities of interest have been added to Section 11.3.2 to reflect current HCV project standards.

11. The summaries of changes from baseline for vital signs have been replaced with summaries of visit values to reflect current HCV project standards (Section 11.4.2).

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. Grundy SM, Brewer HB Jr, Cleeman JI, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004;109(3):433-8.
3. 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.

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