16.1__9 Documentation of Statistical Methods

16.1__9.1 Statistical Analysis Plan

1.0 Title Page

Statistical Analysis Plan

Study M16-156

A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment-Naïve Adults in Brazil with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection

Date: 29 Jan 2019

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 Study M16-156. Study M16-156 evaluates the efficacy and safety of GLE/PIB in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis (fibrosis stage of F2 – F3) for an 8-week treatment duration or with compensated cirrhosis (fibrosis stage F4) for a 12-week treatment duration.

This SAP (Version 1.0) provides details to further elaborate the statistical methods outlined in Clinical Study Protocol M16-156 incorporating Amendment 1 and 2 dated 02 August 2018, and describes analysis conventions to guide the statistical programming. Analyses will be performed using SAS® Version 9.4 (SAS Institute, Inc., Cary, NC 27513) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks following therapy) and safety of GLE/PIB combination in treatment-naïve adults in Brazil with chronic hepatitis C virus (HCV) genotype (GT) 1 – 6 infection without cirrhosis or with compensated cirrhosis. The efficacy and safety endpoints will be analyzed on the overall population (i.e., across treatment durations and genotypes).

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

- The percentages of subjects with HCV on-treatment virologic failure (OTVF);
- The percentages of subjects with HCV virologic relapse.

4.2 Design Diagram

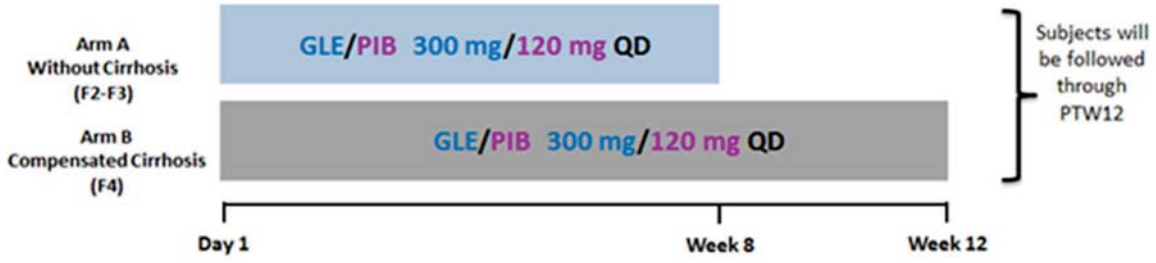
This is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of GLE/PIB for an 8- or 12-week treatment duration in adults in Brazil with chronic HCV GT1 – 6 infection, without cirrhosis or with compensated cirrhosis with a METAVIR System Fibrosis Score of F2, F3 or F4 (F2 - F4) or equivalent, who are HCV treatment-naïve. Approximately 100 subjects meeting the eligibility criteria will be enrolled. The study enrollment will be monitored to meet the following enrollment criteria: 1) a minimum of approximately 35 GT1 and 25 GT3 subjects and 2) approximately 80 F2 – 3 and a maximum of approximately 20 F4 subjects.

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

- Arm A: HCV GT 1 – 6 without cirrhosis (F2 – F3) subjects will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 8 weeks.
- Arm B: HCV GT 1 – 6 subjects with compensated cirrhosis (F4) will be treated with GLE/PIB 300 mg/120 mg once daily (QD) for 12 weeks.

A study schematic is shown below in Figure 1.

Figure 1. Study Design



4.3 Sample Size

It is anticipated that a total of approximately 100 HCV infected treatment naïve GT1 – 6 subjects will be enrolled in this study. No formal hypothesis is being tested. If

the observed SVR_{12} rate in this study is 97% among 100 HCV GT1 – 6 treatment naive subjects, then the half-width of 2-sided 95% normal approximation to the binomial distribution confidence interval will be 3.3% (EAST 6.4).

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.

An interim data lock may occur in the study if interim study results are needed for regulatory interaction purposes. No changes to the study design or treatment of subjects would result from this interim analysis; therefore, no adjustment for multiplicity is needed.

The end-of-study analysis will be conducted when all subjects enrolled in the study have completed the Post-Treatment Week 12 Visit or prematurely discontinued from the study. Data will be locked after performing appropriate data cleaning. Results from this analysis (e.g., SVR_{12} data) will be described in the final clinical study report (CSR).

5.0 Analysis Populations

5.1 Definitions of Analysis Populations

5.1.1 Intention-to-Treat (ITT) Population

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

5.1.2 Modified Intention-to-Treat (mITT) Populations

Sensitivity analyses of SVR_{12} as described in Section 10.5 will be performed on the ITT population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-VF).

5.1.3 Safety Population

All subjects who receive at least one dose of study drug will be included in the safety population. Safety analysis will be performed on the overall 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 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. If multiple measurements that are prior to dosing are recorded on the same date, then the average of these measurements will be considered as the baseline value.

The same baseline value will be used for analyses of the Treatment and Post-Treatment Periods.

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

6.1.2 Study Days

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

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

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

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

Final Treatment Value

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

Final Post-Treatment Value

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

6.2 Definition of Analysis Windows

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

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

If more than one assessment are included in a time window, the assessment closest (except in analyses of SVR) to the nominal time will be used. If there are two observations equally distant to the nominal time, the latest one will be used in analyses. For analyses of SVR (e.g., 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 and Resistance Endpoints, Safety Laboratory and Vital Sign Measurements, Child Pugh Scores and PRO Instruments (Treatment Period)

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Day 1/Baseline[a]	1	≤ 1[a]
Week 4	28	2 to 42
Week 8	56	43 to 70
Week 12[b]	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 12-week treatment duration 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 and End of Treatment Visit, which can be at Week 8, or 12 depending on treatment assignment, or Premature Discontinuation Visit.

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

Scheduled Visit[a]	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Day Range)
Post-Treatment Week 4	28	3 to 56
Post-Treatment Week 12	84	57 to 126
SVR_4[b]	28	3 to 56
SVR_{12}[b]	84	57 to 126

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 and SVR_{12}. For all windows, data must occur after Study Drug End Day 2. Study Drug End Day 0 is defined as the day of the last dose of study drug.

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

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

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

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

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

6.3 Missing Data Imputation

Missing Data Imputation for SVR

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

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

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

Missing Data Imputation for Virologic Failure

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

Missing Data Imputation for PRO Questionnaires

If a respondent answers at least 50% of the items in a multi-item scale of the 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. For TSQM, if a respondent answers at least 2 items in the 3 item scales of Side Effects or Effectiveness, the missing items will be imputed with the average score of the answered items in the same scale. For EQ-5D-3L, health state index and VAS scores no imputation will be performed for missing items.

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

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

7.1 Demographic and Baseline Characteristics

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

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

Categorical demographic and baseline characteristics include:

- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Sex (male or female);

- Race (White, Black/African-American, Asian, American Indian or Alaska Native, or Native Hawaiian or Other Pacific Islander) and black race (black or non-black);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Baseline BMI (< 30 or ≥ 30 kg/m^2);
- HCV genotype and subtype (using central laboratory results and final genotype/subtype results, see Section 10.8);
- Cirrhosis status (yes/no);
- Chronic Kidney Disease stage (Stage 1, 2, 3, 4, or 5);
- Baseline HCV RNA level (< 1,000,000; ≥ 1,000,000 to < 2,000,000; or ≥ 2,000,000 IU/mL);
- Baseline platelet count (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline eGFR (< 15, ≥ 15 to < 30, ≥ 30 to < 45, ≥ 45 to < 60,or ≥ 60 mL/min/1.73 m^2);
- Baseline creatinine clearance (< 15, ≥ 15 to < 30, ≥ 30 to < 45, ≥ 45 to < 60, or ≥ 60 mL/min);
- Baseline fibrosis stage (equivalent to Metavir F0 - F1, F2, F3, or F4);
- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no);
- Tobacco use (current, former, never, or unknown);
- Alcohol use (current, former, never, or unknown);
- Injection drug use (yes, within last 12 months; yes, more than 12 months ago; or no);
- Use of stable opiate substitution (yes/no);
- History of diabetes (yes/no);
- History of depression or bipolar disorder (yes/no);
- History of bleeding disorders (yes/no);
- History of cardiovascular disease (yes/no);

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.

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

Baseline CKD categorization is defined according to eGFR as shown in Table 4 below:

Table 4. Definition of Chronic Kidney Disease Stages

CKD Stage	eGFR (mL/min/1.73 m^2)*
1	≥ 90
2	60 to < 90
3	30 to < 60
4	15 to < 30
5	< 15 or requiring dialysis

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

Subjects will be determined to be requiring dialysis based on the Medical History (MH) eCRF. Requiring dialysis is defined as having medical history coded with any of the Preferred Terms or Lowest Level Terms specified Table 5.

Table 5. Dialysis Related Preferred Terms and Lowest Level Terms

Category	Preferred Term	Lowest Level Term
Dialysis	Artificial kidney device user	Haemodialysis fistula thrombosis
	Dialysis	Dialysis access malfunction
	Dialysis device insertion	Dialysis induced hypertension
	Haemodialysis	Hypotension during dialysis
	Haemofiltration	Thrombosis prophylaxis in hemodialysis
	Peritoneal dialysis	Dialysis device complication
	Renal replacement therapy	Dialysis dementia
	Bloody peritoneal effluent	Dialysis efficacy test
	Dialysis amyloidosis	Dependence on renal dialysis
	Dialysis disequilibrium syndrome	Artificial kidney clotting during dialysis
	Dialysis membrane reaction	Blood leak in dialyser
	Dialysis related complication	
	Extensive interdialytic weight gain	
	Haemodialysis complication	
	Haemodialysis-induced symptom	
	Inadequate haemodialysis	
	Intradialytic parenteral nutrition	
	Peritoneal cloudy effluent	
	Peritoneal dialysis complication	
	Peritoneal effluent abnormal	
	Peritoneal effluent erythrocyte count increased	
	Peritoneal effluent leukocyte count increased	
	Ultrafiltration failure	

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 6.

Table 6. 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 0.72
F4	4	≥ 5	≥ 12.5	≥ 0.73

* 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.

Presence or absence of cirrhosis will be determined as collected in EDC which includes the instructions, "Please indicate the subject's Metavir system fibrosis score" – "F2 - F3" is considered as non-cirrhotic and "F4" is considered cirrhotic."

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

CrCl (mL/min) = [(140 – age) × (weight in kg) × (0.85 if female)]/[serum creatinine (mg/dL) × 72].

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

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

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

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

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

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

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 7.

Table 7. 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)

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

* None;
Slight ascites = Ascites detectable only by ultrasound examination;
Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen;
Severe ascites = Large or gross ascites with marked abdominal distension.

** None: normal consciousness, personality, neurological examination, electroencephalogram;
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves;
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves;
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves;
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

7.2 Medical History

Medical history 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.

Medical history data will be summarized and presented by primary MedDRA System Organ Class (SOC) and Preferred Term (PT). The SOCs will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC.

The number and percentage of subjects with a particular preferred term will be summarized. Subjects reporting more than one preferred term within a SOC will be counted only once for that SOC.

Histories of diabetes, bleeding disorders, depression or bipolar disorder, and cardiovascular disease will be defined by a subject having medical history coded to at least one preferred term within any of the high level terms specified for the category in Table 8.

Table 8. Medical/Surgical History eCRF

Medical History eCRF	
Category	**MedDRA High Level Term Name**
Diabetes	Diabetic complications cardiovascular Diabetic complications dermal Diabetic complications gastrointestinal Diabetic complications NEC Diabetic complications neurological Diabetic complications ophthalmic Diabetic complications renal Diabetes mellitus (incl subtypes) Hyperglycaemic conditions NEC
Bleeding disorders	Coagulation factor deficiencies Coagulopathies Platelet disorders NEC Thrombocytopenias Coagulation disorders congenital

Table 8. Medical/Surgical History eCRF (Continued)

Medical History eCRF	
Category	**MedDRA High Level Term Name**
Depression or bipolar disorder	Depressive disorders Bipolar disorders Mood alterations with manic symptoms
Cardiovascular disease	Coronary artery disorders NEC Ischaemic coronary artery disorders Cardiac conduction disorders Rate and rhythm disorders NEC Supraventricular arrhythmias Ventricular arrhythmias and cardiac arrest Congenital cardiac malpositions and transpositions Congenital cardiac structural defects NEC Congenital cardiovascular disorders NEC Cardiac disorders congenital NEC Cardiac hypoplasias congenital Cardiac malpositions congenital Cardiac septal defects congenital Cardiac valve disorders congenital Cardiovascular disorders congenital NEC Great vessel disorders congenital Multiple cardiac abnormalities congenital Persistent foetal circulation disorders Heart failure signs and symptoms Heart failures NEC Left ventricular failures Right ventricular failures Accelerated and malignant hypertension Renal hypertensions Vascular hypertensive disorders NEC Coronary necrosis and vascular insufficiency Infectious myocarditis Noninfectious myocarditis Peripheral vasoconstriction, necrosis and vascular insufficiency Aortic valvular disorders Cardiac valve disorders NEC Mitral valvular disorders Pulmonary valvular disorders Tricuspid valvular disorders Aortic inflammatory disorders Arterial inflammations Vasculitides NEC

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 either as (1) 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 (2) 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 failure 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.

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

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

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

9.0 Study Drug Exposure and Compliance

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

9.1 Exposure

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

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

- 1 to 15 days
- 16 to 30 days
- 31 to 45 days
- 46 to 60 days
- 61 to 75 days
- 76 to 90 days
- > 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

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

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

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

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

Sensitivity analyses will be conducted for it using the mITT-VF populations.

Missing data will be imputed as described in Section 6.3 for analyses of the HCV RNA endpoints of SVR 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 active 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 active 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 active study drug (up to and including the SVR_{12} window) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment (as defined below), excluding HCV 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 Post-Treatment Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment (as defined below), excluding HCV reinfection.

Virologic failure rate for SVR_{12} = any subject who experiences **On-treatment virologic failure** or **$Relapse_{12}$** out of all ITT subjects.

Only subjects who have at least one post-treatment HCV RNA value will be included in analyses of relapse.

Completion of treatment: For the analysis of relapse, completion of treatment is defined as 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: HCV reinfection is defined as confirmed HCV RNA ≥ LLOQ after the end of active treatment in a subject who had HCV RNA < LLOQ at Final Treatment Visit, along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis of the NS3 or NS5A,

and/or NS5B gene sequences. Reinfection in the case of the same HCV subtype is defined as a clade switch, as indicated by the lack of clustering between the baseline and post-treatment sequences by phylogenetic analysis. If phylogenetic analysis is not possible due to technical difficulties, HCV reinfection may be determined with a confirmed HCV genotype or subgenotype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Post-treatment relapse is defined as described earlier (**Relapse$_{12}$ and 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);
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 Arm A and < 77 days for Arm B] and did not meet the **On-treatment virologic failure or 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]).

For the reasons for SVR_{12} nonresponse defined above, subjects are only to be counted in 1 category. Specifically, subjects who were SVR_{12} 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 or $relapse_{12}$.

10.2 Handling of Multiplicity

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

10.3 Primary Efficacy Analysis

The primary efficacy endpoint is the percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) based on the overall ITT population. 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 the 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 HCV on-treatment virologic failure (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during

treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and

- The percentage of subjects with $Relapse_{12}$ (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment; excluding subjects who have been shown to be reinfected).

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

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

10.5 Sensitivity Analyses for SVR

The two-sided 95% confidence interval using Wilson's score method will also be calculated as a sensitivity analysis for the primary endpoint of SVR_{12} based on ITT population.

As sensitivity analyses, the number and percentage of subjects in the mITT-VF population achieving SVR_{12} will be summarized by genotype and overall, along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution and a two-sided 95% confidence interval using the Wilson's score method. Listings of subjects excluded from mITT-VF population will be provided, as applicable.

10.5.1 Imputation Approaches

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

10.6 Efficacy Subgroup Analysis

The percentage of subjects with SVR_{12} in the ITT population will be calculated with the corresponding two sided 95% Wilson score intervals, for the following subgroups:

- HCV genotype and available subtype (based on final HCV genotype and subtype determination);
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Sex (male or female);
- Race (White, Black/African-American, Asian, or other) and black race (black or non-black);
- Baseline BMI (< 30, or ≥ 30 kg/m^2);
- Baseline HCV RNA level (< 1,000,000 ≥ 1,000,000 to < 2,000,000; or ≥ 2,000,000 IU/mL);
- Baseline fibrosis stage (equivalent to Metavir F2, F3, or F4);
- Cirrhosis Status (yes/no)
- Baseline platelet count (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline creatinine clearance (< 15, ≥ 15 to < 30, ≥ 30 to < 60, ≥ 60 to < 90, or ≥ 90 mL/min);
- Baseline eGFR (< 15, ≥ 15 to < 30, ≥ 30 to < 60, ≥ 60 to < 90, or ≥ 90 mL/min/1.73 m^2);
- History of diabetes (yes/no);
- Subject on 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

The following additional efficacy endpoints will be summarized for 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 with SVR_4;

The percentage of subjects with virologic failure through Post-Treatment Week 12. The number and percentage of subjects meeting each additional efficacy endpoint will be calculated along with a two-sided 95% CI using the Wilson's score method. Imputations for missing data will be performed as described in Section 6.3 for analysis of SVR, virologic failure, and relapse. The first bulleted endpoint above will be presented using data as observed.

A summary of the subjects who completed treatment and relapsed (defined as **$Relapse_{12}$**) will be prepared displaying the number of subjects relapsing overall and by SVR visit window (within the SVR_4, SVR_{12} windows or after SVR_{12} window), including the subject number and the SVR visit window corresponding to the first HCV RNA value of those indicating the occurrence of relapse. A similar summary will be prepared for subjects who prematurely discontinued treatment and relapsed after having HCV RNA < LLOQ at their Final Treatment Visit. A listing of subjects in the ITT population excluded from the relapse denominator (e.g., study drug duration < 52 days for subjects assigned to 8 weeks of treatment, study drug duration < 77 days for subjects assigned to 12 weeks of treatment, or no post treatment HCV RNA) will be provided, as applicable.

A listing of subject numbers and reasons for non-response to SVR_{12} will be prepared.

The concordance between SVR_4 and SVR_{12} will be assessed for the overall population (across treatment arms) by the agreement between SVR_4 and SVR_{12} and the positive predictive value (PPV) and negative predictive value (NPV) of SVR_4 on SVR_{12}. The agreement between SVR_4 and SVR_{12} is a percentage defined as the number of subjects achieving both SVR_4 and SVR_{12} and the number of subjects where both SVR_4 and SVR_{12}

are not achieved. The PPV of SVR_4 on SVR_{12} is the proportion of subjects who achieve SVR_{12} out of all subjects who achieved SVR_4. The NPV of SVR_4 on SVR_{12} is the proportion of subjects who do not achieve SVR_{12} out of all subjects who did not achieve SVR_4.

10.8 HCV Resistance Analyses

For all subjects, full length NS3/4A and NS5A from baseline samples will be sequenced by next generation sequencing (NGS). For subjects who experience virologic failure (on-treatment virologic failure or post-treatment relapse as defined in Section 10.1), full length NS3/4A and NS5A from the first sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. Subjects treated with study drug who do not achieve SVR_{12} due to reasons other than virologic failure (i.e., 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.

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

For each DAA target, signature amino acid positions and a key subset of amino acid positions for the respective inhibitor class are listed in Table 9. Appropriate subtype-specific prototypic reference sequence will be used for comparison with sequences from samples.

Table 9. Signature Amino Acid Positions and the Key Subset of Amino Acid Positions

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

Included time points for analyses on samples from subjects who do not achieve SVR_{12} are 1) the sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1000 IU/mL, and 2) 12 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 (NS3/4A or NS5A).
- Substitution at signature amino acid position: substitution (relative to reference) present at a detection threshold of ≥ 2% or ≥ 15% (depending on frequency threshold utilized) within a subject's viral population 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 polymorphism: polymorphism present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post baseline % – baseline %) ≥ 20].
- Treatment-emergent substitution: A post-baseline substitution or an enriched polymorphism.

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

- By-subject listings of all baseline polymorphisms at signature amino acid positions for each DAA target (NS3/4A and NS5A) at detection thresholds of 2% and 15%.
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15%.
- Total number and percentage of subjects with baseline polymorphisms at a key subset of amino acid positions in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A, by subtype, and total (include all subtypes).

Analysis 2: The impact of baseline polymorphisms on treatment outcome will be assessed as follows: for each polymorphism, the 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%.

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, and the rates with or without polymorphisms will be compared using Fisher's exact test. Analysis will be separated by HCV subtype.

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 substitutions at signature amino acid positions (relative to reference sequence) will be provided for each DAA target (NS3/4A 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.

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

phylogenetic analysis also will be provided. Listing of HCV genotype and subtype will be provided separately for central laboratory results and phylogenetic analysis results.

10.9 Patient Reported Outcomes

The SF-36v2 is a general Health Related Quality of Life (HRQoL) instrument with extensive use in a broad variety of health conditions and is the standard in literature for HCV. The SF-36v2 instrument comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Domain scores are also aggregated into a Physical Component Summary score and a Mental Component Summary score. Higher SF-36v2 scores indicate a better state of health.

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). TSQM scores range from 0 – 100 with higher scores indicating better satisfaction.

The EQ-5D-3L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-3L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 3 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subjects also rate their perception of their overall health on a separate visual analogue scale (VAS).

The mean change from baseline to each applicable post-baseline timepoint in the SF-36v2 Mental Component Summary (SF-36-MCS) and Physical Component Summary (SF-36-PCS) scores; EQ5D-3L health state index and VAS score will be summarized descriptively at each applicable visit and for change from baseline to each applicable visit.

The following analyses of patient reported outcomes (PROs) also will be performed:

- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable timepoint of greater than or equal to 1/2 standard deviation (SD) at baseline points in the SF-36 MCS, PCS and SF-36 domain scores[2,3]

TSQM Effectiveness, Side Effects, Convenience, and Global Satisfaction scores will be summarized descriptively at each applicable visit.

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

11.0 Safety Analysis

11.1 General Considerations

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

11.2 Analysis of Adverse Events

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

11.2.1 Treatment-Emergent Adverse Events

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

11.2.2 Tabulations of Treatment-Emergent Adverse Events

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

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

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 Event Overview

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

- Any treatment-emergent AE;
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Treatment-emergent AEs of grade 3 or higher;
- Treatment-emergent AEs of grade 3 or higher with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);

- Treatment-emergent AEs leading to discontinuation of study drug;
- DAA-related treatment-emergent AEs leading to discontinuation of study drug;
- Serious treatment-emergent AEs leading to discontinuation of study drug;
- Treatment-emergent AEs leading to interruption of study drug;
- Treatment-emergent AEs leading to death;
- Deaths.

Adverse Events by SOC and PT

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

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

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

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

11.2.3 Adverse Events of Special Interest

Adverse events of special interest include the following:

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

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

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

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

11.2.4 Listings of Adverse Events

The following listings of AEs will be prepared:

- All serious AEs (from the time the subject signed the study-specific informed consent through the end of the study),
- Treatment-emergent serious AEs,
- Treatment-emergent AEs leading to 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, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT).

Chemistry variables to be summarized include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, alanine aminotransferase (ALT), aspartate

aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, total protein, glucose, albumin, chloride, bicarbonate, magnesium, gamma-glutamyl transferase (GGT), creatinine clearance (calculated using Cockcroft-Gault), and eGFR by MDRD.

The definitions of toxicity grades for laboratory parameters are presented in Table 10.

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

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
AST	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Alkaline Phosphatase	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Total Bilirubin	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN
Hemoglobin	< LLN – 100 g/L	< 100 – 80 g/L	< 80 g/L	--
Absolute Neutrophil Count	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
Platelet count	< LLN – 75.0 × 10^9/L	< 75.0 – 50.0 × 10^9/L	< 50.0 – 25.0 × 10^9/L	< 25.0 × 10^9/L
INR	> 1 – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	--
Creatinine clearance	< LLN – 60 mL/min	< 60 – 30 mL/min	< 30 – 15 mL/min	< 15 mL/min
Albumin	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	--
White blood cells	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Lymphocyte	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L
GGT	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Glucose (high)	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L	> 27.8 mmol/L
Glucose (low)	< LLN – 3.0 mmol/L	< 3.0 – 2.2 mmol/L	< 2.2 – 1.7 mmol/L	< 1.7 mmol/L
Creatinine	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 6 × ULN	> 6 × ULN
Cholesterol	> ULN – 7.75 mmol/L	> 7.75 – 10.34 mmol/L	> 10.34 – 12.92 mmol/L	> 12.92 mmol/L
aPTT	> ULN – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	--
Sodium (low)	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L
Sodium (high)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L	> 160 mmol/L
Potassium (low)	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L
Potassium (high)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L	> 7.0 mmol/L
Magnesium (low)	< LLN – 0.5 mmol/L	< 0.5 – 0.4 mmol/L	< 0.4 – 0.3 mmol/L	< 0.3 mmol/L
Magnesium (high)	> ULN – 1.23 mmol/L	--	> 1.23 – 3.30 mmol/L	> 3.30 mmol/L

11.3.2 Statistical Methods

The baseline value for clinical laboratory tests will be the last non-missing measurement on or before the day of the first dose of study drug. Values on Day 1 must also be before the time of first dose if time is available. The same baseline value will be used for changes at Treatment Period visits and changes at Post-Treatment Period visits.

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

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

The laboratory parameters listed in Table 11 will be assigned a toxicity grade of 1, 2, 3, or 4. The number and percentage of subjects with a maximum toxicity grade of 1, 2, 3 or 4 will be tabulated. To be counted, the post-baseline value must have a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value. For each laboratory parameter in Table 11, 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 11.

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 (i.e., will not require confirmation). The ratio of direct to total bilirubin will be calculated using the same date/time sample corresponding to the total bilirubin elevation.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

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

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

Table 11. Criteria for Potentially Clinically Significant Vital Sign Values

Test/Measurement	Very Low (VL)	Very High (VH)
Systolic Blood Pressure	≤ 90 mmHg AND A decrease of ≥ 20 mmHg from baseline	≥ 180 mmHg AND An increase of ≥ 20 mmHg from baseline
Diastolic Blood Pressure	≤ 50 mmHg AND A decrease of ≥ 15 mmHg from baseline	≥ 105 mmHg AND An increase of ≥ 15 mmHg from baseline
Pulse Rate	≤ 50 bpm AND A decrease of ≥ 15 bpm from baseline	≥ 120 bpm AND An increase of ≥ 15 bpm from baseline
Weight	A decrease of ≥ 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 at Treatment Period visits and changes at Post-Treatment Period visits.

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

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

11.5 Analysis of Child-Pugh Score

For subjects with compensated cirrhosis, Child-Pugh scores will be categorized as 5, 6, > 6, or missing at baseline and each protocol-specified post-baseline visit, including applicable post treatment visits. Shift tables from baseline to each post-baseline visit will

be created for the cirrhotic subjects in the safety population. The shift tables will cross-tabulate the frequency of subjects with baseline values in each category versus the post-baseline categories. For each baseline category and across the baseline categories, the percentage of subjects in each post-baseline category (excluding the post-baseline category of missing) will be calculated.

12.0 Summary of Changes

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

- Remove demographic and baseline characteristic analyses, subgroup analysis related to HCV/HIV Co-infection subjects because no HCV/HIV Co-infection subjects enrolled

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. Wyrwich KW. Minimal important difference thresholds and the standard error of measurement: is there a connection?. J Biopharm Sta. 2004;14(1):97-110.
3. Rejas J, Pardo A, Ruiz MA. Standard error of measurement as a valid alternative to minimally important difference for evaluating the magnitude of changes in patient-reported outcomes measures. J Clin Epidemiol. 2008;61(4):350-6.

Document Approval

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[redacted]	29-Jan-2019 08:16:21 PM	Approver
	29-Jan-2019 09:00:23 PM	Author
	29-Jan-2019 09:04:53 PM	Approver
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16.1__9.2 PMQ Preferred Terms

CMQ NAME	PREFERRED TERM	MEDDRA VERSION	CMQ VERSION	PREFERRED TERM CODE	CMQ CODE
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Acute hepatic failure	21.1	21.1.3	10000804	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Acute on chronic liver failure	21.1	21.1.3	10077305	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Ascites	21.1	21.1.3	10003445	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Bacterascites	21.1	21.1.3	10068547	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Coma hepatic	21.1	21.1.3	10010075	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Gastric varices haemorrhage	21.1	21.1.3	10057572	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Hepatic encephalopathy	21.1	21.1.3	10019660	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Hepatic failure	21.1	21.1.3	10019663	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Hepatic hydrothorax	21.1	21.1.3	10067365	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Hepatorenal failure	21.1	21.1.3	10019845	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Hepatorenal syndrome	21.1	21.1.3	10019846	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Intestinal varices haemorrhage	21.1	21.1.3	10078058	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Liver transplant	21.1	21.1.3	10024714	80000172

CMQ NAME	PREFERRED TERM	MEDDRA VERSION	CMQ VERSION	PREFERRED TERM CODE	CMQ CODE
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Minimal hepatic encephalopathy	21.1	21.1.3	10076204	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Oesophageal varices haemorrhage	21.1	21.1.3	10030210	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Paracentesis	21.1	21.1.3	10061905	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Peritonitis bacterial	21.1	21.1.3	10062070	80000172
Hepatic Decompensation and Hepatic Failure (Anti-Hepatitis C Virus Product Specific)	Subacute hepatic failure	21.1	21.1.3	10056956	80000172