1.0 Title Page

Statistical Analysis Plan

Study M16-133

A Single Arm, Open Label, Multicenter Study to Evaluate the Efficacy and Safety of Glecaprevir (GLE)/Pibrentasvir (PIB) in Treatment Naïve Adults with Chronic Hepatitis C Virus (HCV) Genotypes 1 – 6 Infection and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 1

Date: 30 Jun 2017

Version 1.0

2.0 Table of Contents

List of Tables

List of Figures

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses for glecaprevir (GLE)/pibrentasvir (PIB) study Protocol M16-133. It provides high level summaries of the planned statistical analyses for key efficacy and safety endpoints and multiplicity control strategy, as well as some programming details that are standard for AbbVie's HCV programs.

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 Background

4.1 Objective

The primary objective of this study is:

- To demonstrate the efficacy (by achieving high SVR_{12} rate) and safety of 8 weeks of treatment with the GLE/PIB combination regimen in treatment-naïve adults with HCV GT1 – GT6 infection with APRI ≤ 1. The primary efficacy objective will be assessed based on mITT population across genotypes HCV GT1 – GT6.

The secondary objectives of this study are:

- To demonstrate the efficacy (by achieving high SVR_{12} rate) of 8 weeks of treatment with the GLE/PIB combination regimen in treatment-naïve adults with HCV GT1 – GT6 infection with APRI ≤ 1 based on ITT population.
- Assess the percentage of subjects with HCV on-treatment virologic failure across genotypes in adults with HCV GT1 – GT6 infection with APRI ≤ 1 based on ITT population.

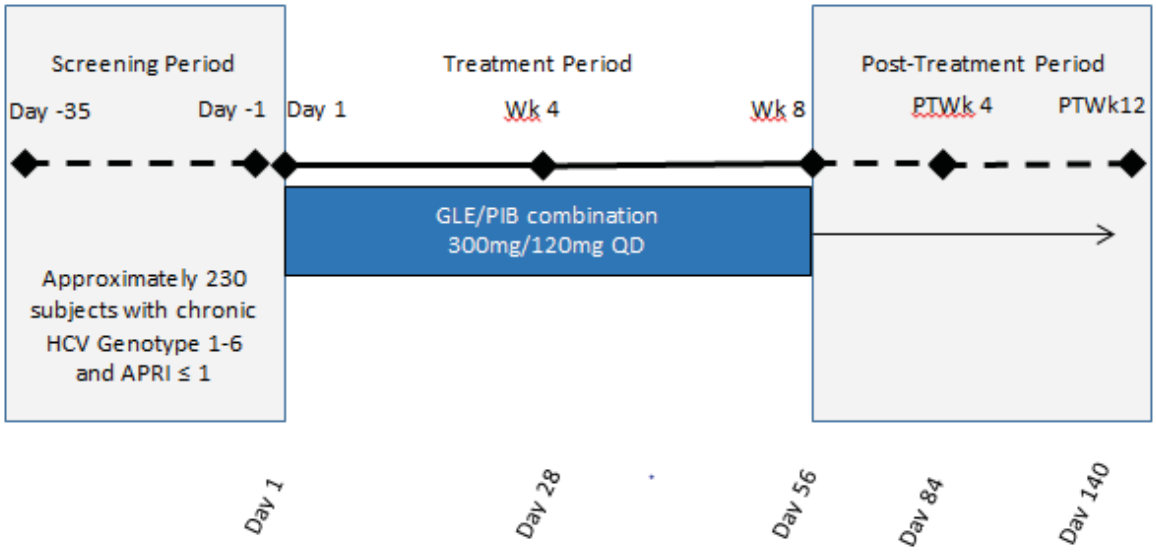
- Assess the percentage of subjects with HCV virologic relapse across genotypes in adults with HCV GT1 – GT6 infection with APRI ≤ 1 based on ITT population.

4.2 Study Design

4.2.1 Study Design and Design Diagram

The schematic of the study is shown in Figure 1. Approximately 230 treatment naïve subjects with chronic HCV GT1 – GT6 and APRI ≤ 1 (maximum of 20% [46] enrollment of GT3-infected subjects), who meet all eligibility criteria, will be enrolled at approximately 43 sites worldwide, and will receive GLE/PIB combination (300 mg/120 mg) QD for 8 weeks in the treatment period and be followed for an additional 12 weeks in the post-treatment period in this non-randomized, open label, Phase 3b study.

Figure 1. Study Design Schematic



4.2.2 Variables Used for Stratification at Randomization (if Applicable)

Not applicable; Study M16-133 is an open label non-randomized study.

4.3 Endpoint

4.3.1 Primary Efficacy Endpoint

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) across genotypes in adults with HCV GT1 – GT6 based on mITT population.

4.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) across genotypes in adults with HCV GT1 – GT6 based on ITT population;
- Percentage of subjects with on-treatment virologic failure based on ITT population;
- Percentage of subjects with post-treatment relapse based on ITT population.

4.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- SVR_{12} in subjects with APRI ≤ 0.7 and in subjects with APRI ≤ 0.5 based on ITT population;
- Percentage of subjects with virologic failure with FibroTest > 0.75 based on ITT population;
- Percentage of subjects with SVR_{12} by key groups (HCV genotype and subtype; age) based on ITT population;
- Adherence to treatment based on ITT population.

4.3.4 Safety Endpoint

Safety evaluations include adverse event (AE) monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG), and clinical laboratory testing (hematology, chemistry including hepatic function parameters) as a measure of safety and tolerability for the entire study duration.

4.4 Sample Size Justification

It is planned to enroll approximately 230 adult subjects with chronic HCV GT1 – GT6 infection with APRI ≤ 1 who are HCV treatment-naïve in the study. The enrollment will be monitored to have approximately maximum 46 GT3-infected subjects (20% of total subjects).

With approximately 230 GT1 – GT6 infected subjects (including 46 GT3 subjects) in mITT analysis, this study has approximately 90% power to demonstrate efficacy of the 8-week treatment in terms of SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 92.4%), assuming that 98% of the GT1, GT2, GT4, GT5, and GT6-infected subjects with APRI ≤ 1 and 94% of the GT3-infected subjects with APRI ≤ 1 achieve SVR_{12}.

With 230 GT1 – GT6 infected subjects (including 46 GT3 subjects) in ITT analysis, this study has approximately 83% power to demonstrate efficacy of the 8-week treatment in terms of SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 91.4%), assuming that 97% of the GT1, GT2, GT4, GT5, and GT6-infected subjects with APRI ≤ 1 and 93% of the GT3-infected subjects with APRI ≤ 1 achieve SVR_{12}.

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

in this study is established by demonstrating the lower boundary of 95% CI for SVR_{12} rate is higher than a cut off value (92.4% and 91.4% for mITT and ITT population, respectively).

In the registration studies different SVR_{12} rates based on mITT population have been observed among naïve non cirrhotic GT3-infected subjects and non-GT3-infected subjects for 8 weeks of GLE/PIB treatment. In these studies, approximately 98.9% and 96.2% SVR_{12} has been observed among non-cirrhotic, treatment naïve chronic HCV GT1, GT2, GT4, GT5, and GT6-infected subjects and GT3 subjects assigned to 8 weeks of treatment, respectively.[1-3] Hence, for the non-cirrhotic GT1 – GT6-infected subjects, based on mITT population, the historical SVR_{12} rate of 98.4% is estimated based on a weighted average of 80% GT1, GT2, GT4, GT5, and GT6 historical rate and 20% GT3 historical rate. To establish cut off for efficacy based on mITT population, a margin of 6% is applied to the historical control rate of 98.4%, resulting in a threshold of 92.4%.

Historical SVR_{12} rate based on ITT population depends on the non-virologic failure in a study. Study-to-study variability has been observed in non-virologic failure rates, and is typically around 1%. The observed rate of non-virologic failure in the registrational program is 1.2% (29/2369).[1-3] For this reason, this study assumes that the historical SVR_{12} rate based on ITT population for treatment naïve non-cirrhotic subjects is 97.4% (with 1% non virologic failure). To establish cut off for efficacy based on ITT population, a margin of 6% is applied to the historical control rate of 97.4%, resulting in a threshold of 91.4%.

4.5 Interim Analysis

There is no interim analysis planned for this study.

4.6 Multiplicity Testing Procedures for Type-I Error Control

In order to control the Type I error rate, a fixed sequence testing procedure will be used for the SVR_{12} endpoints (primary and controlled-secondary efficacy tests of SVR_{12}). Only if success has been demonstrated for the primary endpoint of SVR_{12} based on mITT

population, will the testing proceed to the first secondary endpoint of SVR_{12} based on ITT population.

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

1. Efficacy of the 8-week treatment duration based on mITT population: If this endpoint is statistically significant, then proceed to the following efficacy endpoint. If this endpoint is not statistically significant then stop the testing procedure and declare that no endpoints in the study met statistical significance.
2. Efficacy of the 8-week treatment duration based on ITT population: If this endpoint is statistically significant, then declare the SVR_{12} endpoint is statistically significant for both mITT and ITT populations. If not, then announce that SVR_{12} endpoint is statistically significant only for mITT population.

4.7 Missing Data Imputation

Missing Data Imputation for SVR

HCV RNA values will be selected for analysis based on the analysis windows defined in Section 8.0.

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

For EQ-5D-5L index and VAS scores, no imputation will be performed for missing items. If a subject starts another treatment for HCV, then all PRO assessment values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses.

5.0 Analysis Populations and Important Subgroups

5.1 Analysis Populations

The modified Intention-to-Treat (mITT) population includes all enrolled subjects who received at least 1 dose of study drug, excluding subjects who did not achieve SVR_{12} for reasons other than virologic failure. The mITT population will be used for the primary efficacy analysis.

The Intention-to-Treat (ITT) population includes all enrolled subjects who received at least 1 dose of study drug. The ITT population will be used for all secondary and exploratory efficacy analysis as well as for baseline analyses.

The Safety Population consists of all subjects who received at least 1 dose of study drug.

5.2 Demographics and Baseline Characteristics

Continuous demographic and baseline characteristics include age, weight, height, body mass index (BMI), baseline $\log_{10}$ HCV RNA level, APRI, creatinine clearance (Cockcroft-Gault calculation), eGFR, platelet count, albumin, CD4+ T-cell count, GGT, 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, or other) and (black or non-black);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Geographic region;
- Country;
- Baseline BMI (< 30 or ≥ 30 kg/m^2);
- Baseline APRI (≤ 0.7 or > 0.7) and (≤ 0.5 or > 0.5);
- HCV genotype (1, 2, 3, 4, 5, or 6) and available subtype;
- Baseline HCV RNA level (< 1,000,000 or ≥ 1,000,000 IU/mL) and (< 6,000,000 or ≥ 6,000,000 IU/mL);
- Baseline FibroTest score (≤ 0.75 or > 0.75) and (≤ 0.48, 0.49 to 0.58, 0.59 to 0.75, or > 0.75);
- Former injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no);
- Subject on stable opiate substitution (yes/no).

Categorical demographic and baseline characteristic variables will be summarized with the number and percentage of subjects. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, maximum and minimum).

5.3 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.

5.4 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.

For the safety population, the number of subjects in each of the following categories will be summarized by investigator 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). Similar summaries will be provided for discontinuations from the study and study drug interruptions. Reasons for study drug interruptions will be presented in the CSR listings.

5.5 Study Drug Exposure and Compliance

5.5.1 Exposure

Duration of exposure to study drug is defined for each subject as the last study drug dose date minus the first study drug dose date plus 1 day. The number and percentage of subjects in the safety population with study drug duration of ≥ 52 days will be summarized.

5.5.2 Compliance

At each visit (starting with the Week 4 visit) during the Treatment Period, the total number of tablets dispensed and returned is recorded. The compliance, defined as adherence for study drug (GLE/PIB) during the treatment period, will be calculated as the percentage of tablets taken relative to the total tablets expected to be taken. The total number of tablets expected to be taken will be equal to the total number of tablets that should have been taken per the protocol for the duration that the subject was in the Treatment Period (date of last dose of study drug – date of first dose of study drug + 1). Study drug interruptions recorded on the eCRF will not be subtracted from the duration. A subject is considered to be compliant (adherent to treatment) if the percentage is between 80% and 120%.

6.0 Efficacy Analyses

6.1 General Considerations

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.**

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.

Post-treatment relapse (i.e., **Relapse$_{12}$**) = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment (defined as study drug duration ≥ 52 days), excluding reinfection.

Virologic failure = On-treatment virologic failure or **Post-treatment relapse (Relapse$_{12}$)**

Only subjects who have at least one post-treatment HCV RNA value will be included in the analysis of relapse. For the analysis of relapse, completion of treatment is defined as any subject with study drug duration of 52 days or greater. If the last available post-treatment value is ≥ LLOQ, then the subject will be considered a relapse (i.e., will not require confirmation).

HCV reinfection is defined as confirmed HCV RNA ≥ LLOQ after the end of treatment in a subject who had HCV RNA < LLOQ at Final Treatment Visit, along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis of the NS3 or NS5A, and/or NS5B gene sequences. Reinfection in the case of the same HCV subtype is defined as a clade switch, as indicated by the lack of clustering between the baseline and post-treatment sequences by phylogenetic analysis. If phylogenetic analysis is not possible due to technical difficulties, HCV reinfection may be determined with a confirmed HCV genotype or subgenotype switch 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. Relapse (defined according to the **Relapse$_{12}$** definition for subjects who complete treatment);
3. 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] and did not meet the **On-treatment virologic failure** or **Relapse$_{12}$** definition);
4. HCV reinfection (see definition described earlier);
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]).

6.2 Primary Efficacy Analysis

The primary efficacy endpoint is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The number and percentage of subjects in the mITT population achieving SVR_{12} will be summarized and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution. If the number of SVR_{12} non-responders is less than five, then the Wilson's score method will be used to calculate the confidence interval. As a sensitivity analysis, Wilson's score method will be used to calculate the confidence interval if the number of SVR_{12} non-responders is greater than or equal to five.

The efficacy of 8-week treatment duration for HCV GT1 – GT6 subjects with APRI ≤ 1 based on mITT population will be established if the lower boundary of two-sided 95% confidence interval for the percentage of subjects achieving SVR_{12} is greater than 92.4%.

A summary of reasons for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse) in the mITT population will be provided. A listing of subjects who do not

achieve SVR_{12} by reason for non-response will also be provided. A listing of subjects excluded from the mITT population will be provided.

6.3 Secondary Efficacy Analyses

The number and percentage of subjects in the ITT population achieving SVR_{12} will be summarized and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution. If the number of SVR_{12} non-responders is less than five, then the Wilson's score method will be used to calculate the confidence interval. As a sensitivity analysis, Wilson's score method will be used to calculate the confidence interval if the number of SVR_{12} non-responders is greater than or equal to five.

The efficacy of 8-week treatment duration for HCV GT1 – GT6 subjects with APRI ≤ 1 based on ITT population will be established if the lower boundary of two-sided 95% confidence interval for the percentage of subjects achieving SVR_{12} is greater than 91.4%.

The number and percentage of subjects, along with two-sided 95% Wilson score intervals, with on-treatment virologic failure (defined as **On-treatment virologic failure**) and with post-treatment relapse (defined as **$Relapse_{12}$**) will be summarized overall for the ITT population.

6.4 Other Efficacy Analyses

The following additional efficacy endpoints will be summarized and analyzed 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;
- Adherence to treatment;
- The percentage of subjects in the ITT population with virologic failure by baseline FibroTest score (≤ 0.75 or > 0.75);
- The percentage of subjects in the ITT population with on-treatment virologic failure by HCV genotype;

- The percentage of subjects in the ITT population with post-treatment relapse by HCV genotype.

In the above analyses, the percentage of subjects with a two-sided 95% Wilson score interval will be summarized. Imputations for missing data will be performed as described in Section 4.7 for SVR, where a missing response will be imputed as a failure after performing the described imputation. All other endpoints will be presented using data as observed.

A summary of the subjects who completed treatment and relapsed will be prepared displaying the number of subjects relapsing overall and by SVR visit window (within the SVR_4 window or within the SVR_{12} window), including the subject number and the SVR visit window corresponding to the first occurrence of relapse. A similar listing will be prepared for subjects who prematurely discontinued treatment and relapsed after having HCV RNA < LLOQ at their Final Treatment Visit.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum; number and percentage) will be presented for exposure during the treatment period. Compliance (adherence) 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 based on data as observed. An additional summary of the percentage of compliant subjects will be provided where subjects who are missing study drug accountability records will be imputed as non-compliant.

6.4.1 Resistance Analysis

The following resistance information will be analyzed for all available baseline samples from subjects in the study: 1) the prevalence of polymorphisms at signature amino acid positions or a key subset of amino acid positions at baseline identified by next-generation sequencing (NGS) will be compared to the appropriate subtype specific prototypic reference sequence; and, (2) a comparison of SVR_{12} rates in subjects with or without

baseline variants will be conducted. For subjects not achieving SVR_{12}, treatment-emergent substitutions at post-baseline time points will be identified by NGS relative to the respective baseline sequence and to a subtype-specific reference sequence.

HCV Genotype/Subtype:

Phylogenetic analysis will be conducted on all available HCV sequences from baseline samples in order to accurately determine HCV subtype.

6.4.2 Patient Reported Outcomes

The EuroQoL-5 Dimensions-5 Level (EQ-5D-5L) is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-5L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 5 levels of severity (no problems, slight problems, moderate problems, severe problems, unable to do/extreme problems). Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies.[4,5] Subjects also rate their perception of their overall health on a separate visual analogue scale (VAS).

Summary statistics (n, mean) at each visit and for change from baseline (n, mean, SD, minimum, and maximum) to each visit will be provided for EQ-5D-5L health index score and VAS score.

6.5 Efficacy Subgroup Analyses

The number and percentage of subjects with SVR_{12} in the ITT and mITT populations will be presented for the following key subgroups:

- Baseline APRI (≤ 0.7 or > 0.7) and (≤ 0.5 or > 0.5);
- HCV genotype (1, 2, 3, 4, 5, or 6) and available subtype;
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Baseline FibroTest score (≤ 0.75 or > 0.75);
- Adherence to treatment (yes/no).

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

7.0 Safety Analyses

7.1 General Considerations

Safety analyses will be performed using the safety population.

7.2 Analysis of Adverse Events

Adverse events 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.

Treatment-emergent adverse events are defined as any adverse event (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 adverse event, 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).

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

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 adverse event;

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

Adverse Events by SOC and PT

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.

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

- Treatment-emergent adverse events;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Serious treatment-emergent adverse events;

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

A listing of treatment-emergent adverse events grouped by body system and preferred term with subject numbers will be provided.

Adverse Events by PT

The number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to PT and sorted by overall frequency. Similar summaries will be provided for Grade 3 or higher treatment emergent adverse events, DAA related treatment-emergent adverse events, DAA-related Grade 3 or higher treatment-emergent adverse events, and DAA-related treatment-emergent serious adverse events.

Adverse Events by Maximum Severity Grade Level

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

the highest grade level (grade 5). In this case, the subject will be counted under the "Grade 5" category.

Adverse Event by Maximum Relationship

Treatment-emergent adverse events also will be summarized by maximum relationship of each preferred term to study drug (DAA), as assessed by the investigator. If a subject has an adverse event 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 adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

Other Adverse Events

The number and percentage of subjects experiencing at least one treatment-emergent adverse event in the search defined by Product MedDRA Query (PMQ) "Hepatic Decompensation and Hepatic Failure" will be presented overall and by SOC and PT. In addition, a listing of treatment-emergent adverse events for subjects meeting the search criterion will be provided.

Listing of Adverse Events

The following listings of adverse events will be prepared:

- All serious adverse events (from the time the subject signed the study-specific informed consent through the end of the study),
- Treatment-emergent serious adverse events,
- Treatment-emergent adverse events leading to death,
- Treatment-emergent adverse events leading to discontinuation of study drug,
- Treatment-emergent adverse events leading to study drug interruption.

7.3 Analysis of Laboratory Data

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses. The protocol-defined hematology, clinical chemistry, and urinalysis laboratory tests will be summarized. Some of the above laboratory variables are calculated by the laboratory vendor including indirect bilirubin, creatinine clearance, and eGFR by MDRD.

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

Mean 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, change from baseline mean, standard deviation, minimum, median, and maximum.

The laboratory parameters defined in Table 1 will be assigned a toxicity grade of 1, 2, 3, or 4. The number and percentage of subjects with a maximum toxicity grade of 1, 2, 3 or 4 will be summarized.

Table 1. 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
Albumin	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	--

Assessment of Hepatotoxicity

The number and percentage of subjects with maximum on treatment lab values meeting the following criteria for potential hepatotoxicity will be summarized:

- ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN;
- ALT ≥ 3 × ULN and total bilirubin < 2 × ULN;
- ALT > 5 × ULN and total bilirubin < 2 × ULN;
- ALT < 3 × ULN and total bilirubin ≥ 2 × ULN.

The number and percentage of subjects with post-baseline values during the Treatment Period meeting the following criteria for hepatic laboratory parameters will be summarized:

- ALT > 5 × ULN and ≥ 2 × baseline;
- AST > 5 × ULN and ≥ 2 × baseline;
- Total bilirubin ≥ 2.0 × ULN and > baseline.

7.4 Analysis of Vital Signs and Weight

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 vital sign findings are presented in Table 2.

Table 2. 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

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

Mean 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, 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 Potentially Clinically Significant (PCS) vital sign values (Table 2) 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.

8.0 Analysis Conventions

Baseline

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

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

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

Study Days

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

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

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. 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.

Definition of Analysis Windows

For efficacy analyses of HCV RNA and resistance, the time windows specified in Table 3 and Table 4 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 laboratory data and vital signs, the time windows specified in Table 3 and Table 5 describes how data are assigned to protocol specified time points.

If more than one assessment is included in a time window, the assessment closest (except in analyses of SVR) to the nominal time will be used. If there are two observations equally distant to the nominal time, the latest one will be used in analyses. For analyses of SVR (e.g., 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 3. Analysis Time Windows for HCV RNA, Resistance Endpoints, Laboratory, Vital Sign Measurements, and PRO Instruments (Treatment Period)

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Day 1/Baseline[a]	1	≤ 1[a]
Week 4	28	2 to 42
Week 8	56	43 to 70
Final Treatment Visit[b]	2 to ≤ 2 days after last dose of study drug	

a. Day of first dose of study drug.

b. The last value within the window will be used to define the Final Treatment Visit value. The upper bound of this Final window is Study Drug End Day ≤ 2.

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used.

Table 4. 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 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 and SVR_{12}. Data must also have Study Drug End Day > 2 for all windows. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Table 5. Laboratory Data, Vital Sign and PRO Instruments Visit Windows (Post-Treatment Period)

Scheduled Time	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Days Range)
Post-Treatment Week 4	28	3 to 56
Post-Treatment Week 12	84	57 to 126
Final Post-Treatment Visit[a]	> 2 days after the last dose of study drug	

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

Note: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day > 2. Vital signs and hematology, chemistry, urinalysis, and coagulation panels are collected at both post-treatment visits. PRO instruments are collected at PTW12/PTDC only.

9.0 Summary of Changes

There have been no changes since the latest version of the protocol.

10.0 References

1. Zeuzem S, Feld J, Wang S, et al. ENDURANCE-1: a phase 3 evaluation of the efficacy and safety of 8- versus 12-week treatment with glecaprevir/pibrentasvir (formerly ABT-493/ABT-530) in HCV genotype 1 infected patients with or without HIV-1 co-infection and without cirrhosis. Hepatology. 2016;64 (Suppl 1):132A.
2. Hassanein T, Wyles D, Wang S, et al. Glecaprevir/pibrentasvir demonstrates high SVR rates in patients with HCV genotype 2, 4, 5, or 6 infection without cirrhosis following an 8-week treatment duration (SURVEYOR-II, Part 4). Hepatology. 2016;64 (Suppl 6):1128A.
3. Foster G, Gane E, Asatryan A, et al. ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naïve HCV genotype 3-infected patients without cirrhosis. J Hepatol. 2017;66 (Suppl 1):S33.
4. Szende A, Williams A. Measuring self-reported population health: an international perspective based on EQ-5D. EuroQol Group Monographs Volume 1. SpringMed Publishing; 2004.
5. Rabin R, Oemar M, Oppe M, et al. EQ-5D-5L user guide: basic information on how to use the EQ-5D-5L instrument, Version 1.0. Rotterdam, the Netherlands: EuroQol Group; 2011.

Document Approval

Study M16133 - Statistical Analysis Plan Version 1 - 30Jun2017 (E3 16.1.9)

Version: 1.0 **Date:** 30-Jun-2017 08:04:27 PM **Company ID:** 06302017-00F9F682A8F26D-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	30-Jun-2017 04:26:53 PM	Approver
	30-Jun-2017 05:27:50 PM	Approver
	30-Jun-2017 08:04:26 PM	Study Director