1.0 Title Page

Statistical Analysis Plan

Study M14-730

A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection and Human Immunodeficiency Virus-1 (HIV-1) Co-Infection (EXPEDITION-2)

14 December 2016

2.0 Table of Contents

List of Tables

List of Figures

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the AbbVie Statistics and Statistical Programming Departments, or designee, for Study M14-730.

Study M14-730 examines the safety and efficacy of treatment with the combination regimen glecaprevir/pibrentasvir for 8 or 12 weeks in HCV genotype 1 – 6 infected subjects with HIV-1 co-infection with or without cirrhosis.

This SAP provides details to further elaborate the statistical methods outlined in Clinical Study Protocol M14-730 Amendment 3 dated 12 July 2016, and describes analysis conventions to guide the statistical programming. Analyses will be performed using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objectives of this study are to compare the SVR_{12} rates (12-week sustained virologic response, SVR_{12} [HCV RNA < LLOQ 12 weeks following therapy]) of 8 or 12 weeks of treatment with glecaprevir/pibrentasvir combination in HCV genotype 1 – 6 infected subjects with HIV-1 co-infection to a pre-defined threshold, based on the historical SVR_{12} rate of the current standard of care (i.e., sofosbuvir/ledipasvir for 12 weeks or grazoprevir/elbasvir for 12 weeks) and to assess the safety of treatment with the combination regimen glecaprevir/pibrentasvir for 8 or 12 weeks in HCV genotype 1 – 6 infected subjects with HIV-1 co-infection.

The secondary objectives are to assess the percentages of subjects with on-treatment HCV virologic failure and the percentages of subjects with post-treatment HCV relapse among HCV genotype 1 – 6 infected subjects with HIV-1 co-infection.

The pharmacokinetics, emergence and persistence of viral variants, maintenance of HIV RNA suppression and emergence of HIV variants will also be assessed for the glecaprevir/pibrentasvir treatment regimen.

4.2 Design Diagram

This is a Phase 3, multicenter, open-label study to evaluate the efficacy and safety of the combination regimen glecaprevir/pibrentasvir in HCV treatment-naïve (i.e., subject has not received a single dose of any approved or investigational anti-HCV medication) or treatment-experienced (i.e., subject who has failed prior IFN or pegIFN with or without RBV therapy, or SOF plus RBV with or without pegIFN) adults with chronic HCV GT1 – 6 infection and HIV-1 co-infection with or without cirrhosis (F0-F4; excluding GT3 treatment-experienced subjects) for an 8-week (non-cirrhotics) or 12-week (cirrhotics) treatment duration.

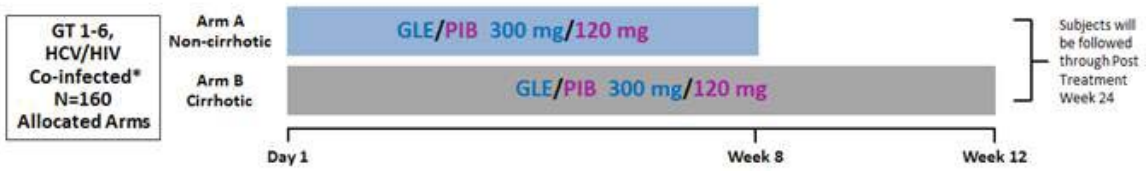
Subjects must be naïve to treatment with any HIV-1 antiretroviral therapy (ART) or on a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to Screening. For cirrhotic subjects, the qualifying HIV-1 ART regimen must contain one of the following ARV agents: rilpivirine (RPV), raltegravir (RAL), dolutegravir (DTG), or elvitegravir/cobicistat (EVG/COBI). For non-cirrhotic subjects, HIV-1 ART regimens containing one of the following ARV agents are also allowed: darunavir co-administered with ritonavir (DRV + RTV) QD, darunavir/cobicistat (DRV/COBI) QD or lopinavir/ritonavir (LPV/r) BID.

The study consists of a Treatment Period and a Post-Treatment (PT) Period.

The study was designed to enroll approximately 160 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

A study schematic is shown below in Figure 1.

Figure 1. Study Design



* HCV GT3 treatment-experienced subjects are not eligible for this study.

Eligible subjects will be allocated to one of the following treatment arms:

- Arm A: HCV GT1 – 6/HIV-1 co-infected non-cirrhotic subjects will be treated with glecaprevir/pibrentasvir 300 mg/120 mg once a day (QD) for 8 weeks.
- Arm B: HCV GT1 – 6/HIV-1 co-infected subjects with compensated cirrhosis will be treated with glecaprevir/pibrentasvir 300 mg/120 mg once a day (QD) for 12 weeks.

4.3 Sample Size

The study plans to enroll approximately a total of 160 subjects. A maximum of approximately 110 HCV GT-1 infected subjects will be enrolled. A minimum of 10% (n = 16) of the overall study population will be subjects with compensated cirrhosis. The primary efficacy endpoint of SVR_{12} will be assessed for the ITT population.

With 160 subjects and assuming that 97% of the subjects achieve SVR_{12}, this study has greater than 90% power to demonstrate non inferiority to the historical control SVR_{12} rate (i.e., a two-sided 95% lower confidence bound above 90%) using a one-sample test for superiority using EAST 6.3. No adjustment for dropout is applicable because subjects who do not have data at Post-Treatment Week 12 (after imputing) are counted as failures for SVR_{12}.

4.3.1 Justification of Success Criteria and Non-Inferiority Margin for SVR_{12}

Efficacy of the glecaprevir/pibrentasvir regimen in this study will be established by demonstrating non-inferiority to a historical control regimen. The SVR_{12} rate of the historical control regimen was calculated, and a threshold was determined by subtracting a non-inferiority margin from the historical SVR_{12} rate. Efficacy will be established if the lower 95% confidence bound of the SVR_{12} rate for the glecaprevir/pibrentasvir regimen is greater than the threshold.

To align with the Phase 3 studies of glecaprevir/pibrentasvir in the HCV mono-infected population, a non-inferiority margin of 6% was chosen for this study. In addition, consideration was given to the fact that limited efficacy data exists for non-GT1 HCV/HIV co-infected patients.

A historical SVR_{12} rate of 96% for the current standard of care will be used and is based on the SVR_{12} rates for sofosbuvir/ledipasvir for 12 weeks (96%; 321/335) and grazoprevir/elbasvir for 12 weeks (96%; 210/218).[1,2] To establish non-inferiority to the historical control, a margin of 6% is applied to the historical control rate of 96%, resulting in a threshold of 90%.

4.4 Primary Analysis

The primary analysis will occur after all subjects have completed the PT Week 12 Visit or prematurely discontinued the study. For the primary analysis, data will be locked after performing data cleaning. Results from the primary analysis (e.g., SVR_{12} data) will be described in the primary clinical study report (CSR) that is planned to be included as part of submissions to regulatory agencies to support possible labeling changes.

The final analysis will be conducted when all subjects enrolled in the study have completed the 24 week post-treatment visit or prematurely discontinued from the study. Data after the primary analysis will be added to a new version of the database which will be cleaned and locked at the end of the study and included in the final CSR.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

5.1.1 Intention-to-Treat (ITT) Population

All enrolled subjects who receive at least one dose of study drug will be included in the ITT population.

Efficacy analyses will be performed on the overall ITT population, combining Arms A and B.

5.1.2 Modified Intention-to-Treat (mITT) Population

Sensitivity analyses of SVR_{12} as described in Section 10.5, when applicable, will be performed on the intention-to-treat population modified to exclude subjects not of eligible genotypes (e.g., subjects of multiple/mixed genotypes or a treatment-experienced subject determined to be HCV GT3 according to Lipa, Sanger or phylogenetic analyses as described in Section 10.8 under HCV Genotype/Subtype) (mITT-GT), and on the mITT-GT population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-VF).

5.1.3 Safety Population

All subjects who receive at least one dose of study drug will be included in the safety population. Safety and demographic analyses will be performed on the safety population. Safety and demographic analyses will be performed for each treatment arm and on the overall safety population, combining Arms A and B.

5.2 Variables Used for Stratification of Randomization

This study is not randomized. Eligible subjects will be enrolled into a treatment arm based on cirrhotic status.

6.0 Analysis Conventions

6.1 Definition of Baseline and End of Treatment Assessment

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 (other than intensive PK samples) are to be performed prior to administering the first dose of study drug. Therefore, all Day 1 assessments for which time is not collected will be assumed to be pre-dose and the baseline value will be the last non-missing measurement collected on or before the first day of study drug administration.

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

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

6.1.2 Study Days

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

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

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

Final Treatment Value

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

Final Post-Treatment Value

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

6.2 Definition of Analysis Windows

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

For samples of plasma HIV-1 RNA levels and flow cytometry (including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]), the time windows specified in Table 3 and Table 4 describes how data are assigned to protocol specified time points.

For laboratory data and vital signs, the time windows specified in Table 1 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}) and the analysis of HIV virologic outcomes at the end of treatment and Post-Treatment Week 12 using the FDA snapshot algorithm, the last value in the window will be used.

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

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

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

a. Day of first dose of study drug.

b. For 12-week treatment 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.

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used. PRO instruments are collected at Day 1 and End of Treatment Visit, which can be at Weeks 8 or 12 depending on treatment assignment.

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 2	14	3 to 21
Post-Treatment Week 4	28	22 to 42
Post-Treatment Week 8	56	43 to 70
Post-Treatment Week 12	84	71 to 126
Post-Treatment Week 24	168	127 to 999
SVR_4[b]	28	3 to 56
SVR_{12}[b]	84	57 to 126
SVR_{24}[b]	168	127 to 210

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

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

Note: The result closest to the scheduled time point will be used, except for SVR_4, SVR_{12}, and SVR_{24}. Data must also have Study Drug End Day > 2 for all windows. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Table 3. Analysis Time Windows for HIV-1 RNA and Flow Cytometry Samples (Treatment Period)

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

a. Day of first dose of study drug.

b. For 12-week treatment 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.

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used. Flow cytometry samples are collected at Day 1, Week 4, and End of Treatment visit, which can be at Weeks 8 or 12 depending on treatment assignment.

Table 4. Analysis Time Windows for HIV-1 RNA and Flow Cytometry Samples (Post-Treatment Period)

Scheduled Visit	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

Note: The result closest to the scheduled time point will be used. 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 2	14	3 to 21
Post-Treatment Week 4	28	22 to 42
Post-Treatment Week 8	56	43 to 70
Post-Treatment Week 12	84	71 to 126
Post-Treatment Week 24	168	127 to 999
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 are collected at every PT visit; hematology, chemistry, urinalysis, and coagulation panels are collected at PTW4 and PTDC (if subject discontinued prior to PTW4). For subjects with compensated cirrhosis at baseline, chemistry and coagulation panels are collected to calculate the Child Pugh Score. PRO instruments are collected at PTW12 and PTW24 only.

6.3 Missing Data Imputation

Missing Data Imputation for SVR

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

For analyses of SVR, subjects' missing visit values will have backward imputation applied, if possible. For backward imputation, if the nearest HCV RNA value after the

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

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

Missing Data Imputation for Virologic Failure

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

Missing Data Imputation for PRO Questionnaires

The handling of missing data for patient reported outcomes (PROs) will be as follows. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. The Mental and Physical Component Summary measures will not be computed if any domain is missing. The missing items of the FSS questionnaire will be imputed with the average score of the answered items as long as more than 50% of the items on the FSS are answered. For EQ-5D-3L index and VAS scores, no imputation will be performed for missing items.

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

The safety population will be used to summarize demographics and baseline characteristics.

The safety population will be used to summarize medical history and previous, concomitant, and post-treatment medications.

7.1 Demographic and Baseline Characteristics

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

Continuous demographic variables include age, weight, height, waist circumference, and body mass index (BMI). Categorical demographic variables include sex, race, black race (black or non-black), ethnicity, age category (< 65 or ≥ 65 years; < 75 or ≥ 75 years), BMI category (< 30, or ≥ 30 kg/m^2), country, and geographic region (North America, Europe, or rest of world [ROW]).

When defining geographic region, sites in the United States and Puerto Rico will be grouped under North America; sites in Belarus, Germany, France, Poland, Russia, and the United Kingdom will be grouped under Europe; sites in Australia will be grouped together as ROW).

Continuous baseline characteristics include baseline $\log_{10}$ HCV RNA level, homeostasis model of assessment – insulin resistance (HOMA-IR), creatinine clearance, eGFR, platelet count, albumin, CD4+ T-cell count, GGT, LDL, HDL, APRI, FIB-4, AST, ALT, total, direct, and indirect bilirubin for all subjects.

Categorical baseline characteristics include:

- HCV genotype (1, 2, 3, 4, 5, or 6) and available subtype (as determined by the central laboratory);
- Prior HCV treatment history (naïve or experienced);
  - For treatment-experienced subjects, type of previous regimen (IFN- or SOF-based);
  - For treatment-experienced subjects, type of non-response to previous treatment (on-treatment nonresponder or breakthrough, post-treatment relapse, or unknown/other);
- Prior HCV DAA treatment history:
  - DAA-naïve (i.e., treatment naïve or treatment-experienced with IFN or pegIFN with or without RBV);
  - DAA-experienced (i.e., treatment-experienced with sofosbuvir with RBV with or without pegIFN);
- HIV-1 treatment status (naïve to ART, on a stable ART);
- HIV-1 ART regimen (for those on stable ART):
  - N(t)RTI Backbone: TDF, TAF, ABC
  - Anchor ARV: RAL, DTG, EVG, RPV, DRV, LPV/r
- Baseline CD4+ T-cell (< 200, 200 to < 350, 350 to < 500, or ≥ 500 cells/mm^3) count;
- IL28B genotype (CC, CT, or TT; CC or non-CC);
- Baseline HCV RNA level (< 1,000,000 or ≥ 1,000,000 IU/mL, < 6,000,000 or ≥ 6,000,000 IU/mL);
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, or F4 [if applicable]);
- Baseline platelet count (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, ≥ 90 mL/min);
- Baseline eGFR (< 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73 m^2);
- History of diabetes (yes/no);

- History of bleeding disorders (yes/no);
- History of depression or bipolar disorder (yes/no);
- History of cardiovascular disease (yes/no);
- Baseline metabolic syndrome (yes/no);
- Injection drug use (yes, within last 12 months; yes, more than 12 months ago; or no);
- Subject on stable opiate substitution (yes/no);
- Tobacco use (user, ex-user, or non-user);
- Alcohol use (drinker, ex-drinker, or non-drinker);
- Concomitant use of Proton Pump Inhibitors (PPIs).

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

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

The last HIV-1 medications taken prior to Day 1, as recorded on the CRF 'ARV Dosing Prior to Visit' will be the data source for the summary of baseline HIV-1 ART regimen.

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

If the IL28B genotype result is not available from a sample collected on Day 1, then a result available from a sample collected at any time during the study will be used to summarize IL28B genotype. IL28B rs12979860 will be resulted as C/C, C/T, or T/T by the central laboratory.

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 < 0.75
F4	4	≥ 5	≥ 12.5	≥ 0.75

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

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

Baseline Child-Pugh score will be calculated according to 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)

* 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.

** Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

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

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

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

Subjects will be classified as having metabolic syndrome if at least 3 of the 5 characteristics in Table 8 are present.

Table 8. Clinical Identification of Metabolic Syndrome

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

Reference: Grundy 2004.[3]

Histories of diabetes, bleeding disorders, depression or bipolar disorder, and cardiovascular disease will be based on the Medical History (MH) eCRF, as defined in Table 9.

Table 9. Medical History eCRF

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

7.2 Medical History

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

than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Prior, Concomitant and Post-Treatment Medications

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

The number and percentage of subjects taking prior medications, concomitant medications, and post-treatment HCV medications will be summarized by generic drug name based on the WHO Drug Dictionary. The prior HCV medications taken by the treatment experienced subjects will be summarized separately from other prior medications.

8.0 Patient Disposition

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

8.1 Disposition of Safety Population

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

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

- Subjects who prematurely discontinued from the study;
- Subjects ongoing in the Post-Treatment Period at the time of the primary analysis.

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

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

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

9.0 Study Drug Exposure and Compliance

9.1 Exposure

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

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

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

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

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

9.2 Compliance

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

A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum for each treatment arm and overall. A listing of compliance for each subject will be provided. The percentage of compliant subjects will be summarized for each treatment arm and overall, based on data as observed. An additional summary of the percentage of compliant subjects, overall and by treatment arm, will be provided where subjects who are missing study drug accountability records will be imputed as non-compliant.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

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

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

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

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

The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 15 IU/mL, including values reported as "HCV RNA NOT DETECTED" or "< 15 IU/ML HCV RNA DETECTED." HCV RNA ≥ 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.

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

$Relapse_{12}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment (defined as study drug duration ≥ 52 days for Arm A, and ≥ 77 days for Arm B), excluding reinfection as described below.

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

$Relapse_{overall}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the PT Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment (defined as study drug duration ≥ 52 days for Arm A, and ≥ 77 days for Arm B), excluding reinfection.

Virologic failure = **On-treatment virologic failure** or **Relapse$_{overall}$**.

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

HCV reinfection is defined as confirmed HCV RNA ≥ LLOQ after the end of treatment in a subject who had HCV RNA < LLOQ at Final Treatment Visit, along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis of the NS3 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$_{12}$**, **Relapse$_{24}$**, **Relapse$_{overall}$**), and no genotype, subtype, or clade switch compared with baseline as determined by phylogenetic analysis of the NS3 or NS5A gene sequences. If phylogenetic analysis is not possible due to technical difficulties, the subject will be defined as having a post-treatment relapse unless an HCV genotype or subgenotype switch is confirmed by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Reasons for SVR$_{12}$ Non-Response

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

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);

2. 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 for subjects in Arm A, and < 77 days for subjects in Arm B] and did not meet the **On-treatment virologic** failure 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]).

Reasons for SVR_{24} Non-Response

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

1. On-treatment virologic failure (see **On-treatment virologic failure definition**);
2. Relapse (defined according to the **Relapse$_{12}$** definition for subjects who complete treatment);
3. Relapsed after achieving SVR_{12} (see **Relapse$_{24}$** definition);
4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{24} non-responder who prematurely discontinued study drug [study drug duration < 52 days for subjects in Arm A, and < 77 days for subjects in Arm B] and did not meet the **On-treatment virologic failure**, **Relapse$_{12}$**, or **Relapse$_{24}$** definitions);
5. HCV reinfection;

6. Missing follow-up data in the SVR_{24} window (defined as any subject who completed study drug without data in the SVR_{24} window after applying the imputation rules and not meeting the definitions of [1], [2], [3], [4], or [5]);
7. Other (defined as any SVR_{24} non-responder not meeting the definitions of [1] – [6]).

10.2 Handling of Multiplicity

There will be no adjustment for multiple comparisons. The primary efficacy analysis includes testing of a single hypothesis and no hypotheses will tested for the secondary efficacy analyses.

10.3 Primary Efficacy Analysis

The primary efficacy endpoint is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in the ITT population. The number and percentage of subjects achieving SVR_{12} will be summarized and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial. If the SVR_{12} rate is 100%, then the Wilson's score method will be used to calculate the confidence interval.

The percentage of subjects treated with glecaprevir/pibrentasvir and achieving SVR_{12} will be non-inferior to the 96% SVR_{12} rate of the current standard of care (i.e., sofosbuvir/ledipasvir for 12 weeks [96%; 321/335][2] or grazoprevir/elbasvir for 12 weeks [96%; 210/218][1]) if the lower confidence bound of the 2-sided 95% confidence interval of the percentage of subjects with SVR_{12} is > 90%.

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

10.4 Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment HCV virologic failure (defined as **On-treatment virologic failure**),
- The percentage of subjects with post-treatment HCV relapse (defined as **$Relapse_{12}$**; subjects with reinfection will be summarized separately).

The number and percentage of subjects with on-treatment virologic failure and post-treatment relapse (**$Relapse_{12}$**) will be summarized along with two-sided 95% Wilson score intervals.

10.5 Sensitivity Analyses for SVR

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

As a sensitivity analysis, a two-sided 95% confidence interval for the SVR_{12} rate in the ITT population will be calculated using a Wilson score interval.

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

10.5.1 Imputation Approaches

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

- imputing any missing HCV RNA values in the SVR_{12} window by carrying forward the last non-missing (post-baseline) HCV RNA value prior to the SVR_{12} window;

- imputing as described in Section 6.3 but treat SVR_{12} non-responders who were categorized as "prematurely discontinued study drug with no on-treatment virologic failure" or "missing follow-up data in the SVR_{12} window" as successes.

The percentage of subjects with SVR_{12} will then be presented along with two-sided 95% normal and Wilson score confidence intervals.

10.6 Efficacy Subgroup Analysis

The percentage (and two-sided Wilson score confidence intervals) of subjects with SVR_{12} in the ITT population will be presented for the following subgroups if data are available:

- HCV genotype (1, 2, 3, 4, 5, or 6) and available subtype (as defined in Section 10.8);
- Prior HCV treatment history (treatment-naïve or treatment-experienced);
  - For treatment-experienced subjects, type of previous regimen (IFN- or SOF-based);
- IL28B genotype (CC or non-CC);
- Sex (male or female);
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Race (White, Black/African-American, Asian, or other) and (black or non-black);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Baseline BMI (< 30, or ≥ 30 kg/m^2);
- Baseline HCV RNA level (< 1,000,000 or ≥ 1,000,000 IU/mL) and (< 6,000,000 or ≥ 6,000,000 IU/mL);
- Cirrhosis status (yes/no);
- Baseline platelet count (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, ≥ 90 mL/min);
- Baseline eGFR (< 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73 m^2);

- Geographic region (North America, Europe, Rest of world);
- Country (as appropriate);
- History of diabetes (yes/no);
- Baseline metabolic syndrome (yes/no);
- Former injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no);
- Subject on stable opiate substitution (yes/no);
- Baseline CD4+ Count (< 200, 200 to < 350, 350 to < 500, or ≥ 500 cells/mm^3);
- Presence of baseline resistance-associated variants (any NS3/4A variant [yes/no]; any NS5A variant [yes/no]; any NS3/4A and any NS5A variant [yes/no], any NS3/4A or any NS5A variant [yes/no]), and (NS3/NS4A variant only, NS5A variant only, both NS3/4A variant and NS5A variant, or none);
- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no).

For subjects with cirrhosis only:

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

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

For the subgroup analyses, the presence of baseline resistance-associated variants as listed above are defined in Section 10.8.1.1.1; this subgroup analysis will be performed in the mITT-GT-VF population.

10.7 Additional 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;

- The percentage of subjects with SVR_{24};
- The percentage of subjects who relapsed after achieving SVR_{12} (**$Relapse_{24}$**);
- The percentage of subjects with virologic failure through Post-Treatment Week 12 (i.e., the SVR_{12} non-responders due to on-treatment virologic failure or $Relapse_{12}$)

In the above analyses for SVR, virologic failure, and relapse, the percentage of subjects with a two-sided 95% Wilson score interval will be summarized. Imputations for missing data will be performed as described in Section 6.3 for analysis of SVR, where a missing response will be imputed as a failure after performing the described imputation. All other endpoints will be presented using data as observed.

The difference of the percentage of subjects achieving SVR_{12} in the ITT population and the SVR_{12} rate of the historical rate for HCV/HIV co-infected subjects (96%) justified in Section 4.3.1 will be calculated with a normal approximation interval.

A summary of the subjects who completed treatment and relapsed (defined as **$Relapse_{overall}$**) will be prepared displaying the number of subjects relapsing overall and by SVR visit window (within the SVR_4, SVR_{12}, SVR_{24} windows or after SVR_{24} window), including the subject number and the SVR visit window corresponding to the first occurrence of relapse. A similar listing will be prepared for subjects who prematurely discontinued treatment and relapsed after having HCV RNA < LLOQ at their Final Treatment Visit.

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

The concordance between SVR_{12} and SVR_{24} will be assessed by the agreement between SVR_{12} and SVR_{24} and the positive predictive value (PPV) and negative predictive value (NPV) of SVR_{12} on SVR_{24}. The agreement between SVR_{12} and SVR_{24} is a percentage defined as the number of subjects achieving both SVR_{12} and SVR_{24} and the number of

subjects where both SVR_{12} and SVR_{24} are not achieved. The PPV of SVR_{12} on SVR_{24} is the proportion of subjects who achieve SVR_{12} and SVR_{24} out of all subjects who achieved SVR_{12}. The NPV of SVR_{12} on SVR_{24} is the proportion of subjects who neither achieve SVR_{12} nor SVR_{24} out of all subjects who did not achieve SVR_{12}. Similarly, the concordance between SVR_4 and SVR_{12} will be summarized.

10.8 Resistance Analyses

10.8.1.1 HCV Drug-Resistance Analyses

For all subjects, full length NS3/4A or NS5A from baseline samples will be sequenced by next generation sequencing (NGS). For subjects who experience virologic failure (on-treatment virologic failure or post-treatment relapse as defined in Section 10.1), full length NS3/4A and NS5A genes from the first sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. An appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples. Subjects who experience virologic failure will be referred to as subjects in the primary virologic failure (PVF) population, and a listing by subject that includes HCV genotype/subtype, IL28B genotype, reason for SVR_{12} non-response, time point(s) sequenced as closest to time of VF, and HCV RNA value at the VF time point(s) will be produced for these subjects. In addition, all listings described below will display HCV genotype/subtype and reason for SVR_{12} non-response in the subject identifier for each subject. A separate listing will summarize all subjects in the PVF population for whom no sequencing was performed (e.g., lost to follow-up while HCV RNA ≤ 1000 IU/mL).

Subjects treated with study drug who do not achieve SVR_{12} due to reasons other than virologic failure (prematurely discontinued study drug with no on-treatment virologic failure, HCV reinfection, missing SVR_{12} data or other reasons as described in Section 10.1, Reasons for SVR_{12} Non-Response), but have a time point with HCV RNA ≥ 1000 IU/mL after treatment discontinuation, will have the sample at that time point sequenced. These subjects will be referred to as the non-PVF population. A listing of all subjects in the non-PVF population with post-baseline sequencing available will be

created that is similar to the listing of subjects in the PVF population with post-baseline sequencing available.

For each DAA target, resistance-associated signature amino acid positions and a key subset of amino acid positions are listed in Table 10. Appropriate subtype-specific prototypic reference sequence will be used for comparison with sequences from samples.

Table 10. List of Genotype-Specific Signature Amino Acid Positions and Key Subsets of Amino Acid Positions

Genotype	Signature Amino Acid Positions	Key Subset of Amino Acid Positions
NS3/4A		
1a	36, 43, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, and 170	155, 156, 168
1b	36, 54, 55, 56, 80, 107, 122, 155, 156, 158, 168, 170, and 175	155, 156, 168
2, 3, 4, 5, 6	36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3 only) and 168	155, 156, 168
NS5A		
1a	24, 28, 29, 30, 31, 32, 58, 62, 92, and 93	24, 28, 30, 31, 58, 92, 93
1b	24, 28, 29, 30, 31, 32, 54, 58, 62, 92, and 93	24, 28, 30, 31, 58, 92, 93
2, 3, 4, 5, 6	24, 28, 29, 30, 31, 32, 58, 92, and 93	24, 28, 30, 31, 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) 24 weeks post-DAA treatment, provided that resistance-associated variants were detected at the time of failure/discontinuation.

The following definitions will be used in the resistance analyses:

- Baseline variant: a variant by NGS in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on variant frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3/4A or NS5A)

- Variant at signature amino acid position: variant (relative to reference) present by NGS at a detection threshold of 2% or 15% (depending on variant frequency threshold utilized) in a baseline or a post-baseline sample at a signature amino acid position
- Post-baseline variant: an amino acid variant in a post-baseline time point sample that was not detected at baseline (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the post-baseline sample
- Enriched variant: variant present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20]
- Treatment-emergent variant by NGS: A post-baseline variant or an enriched variant

Analysis will be performed separately for each HCV genotype/subtype within each listing.

Analysis 1: The following analyses will be performed for all subjects:

- A listing of all baseline variants (2% detection threshold) at signature resistance-associated amino acid positions for each DAA target (NS3/4A and NS5A) (ITT).
- A listing of all baseline variants (15% detection threshold) at non-signature resistance-associated amino acid positions for each DAA target (NS3/4A and NS5A) for subjects in PVF population.
- The number and percentage of subjects with baseline variants at detection-thresholds of 2% and 15% for variants at signature amino acid positions (ITT). This table includes prevalence of each baseline variant, and a summary of the number of subjects with variants in NS3 only, NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, and any in NS3 + NS5A.
- Total number and percentage of subjects with baseline polymorphisms ***at a key subset of amino acid positions*** in NS3 only, NS5A only, any in NS3, any in

NS5A, any in NS3 or NS5A, and any in NS3 + NS5A (ITT), by subtype, and total.

- Total number and percentage of subjects with baseline polymorphisms ***at a key subset of amino acid positions*** in NS3 only, NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, and any in NS3 + NS5A (ITT), by genotype, and total.

Analysis 2: The impact of baseline variants on treatment outcome will be assessed for **mITT-GT-VF** population as follows: for each variant, the SVR_{12} rate will be calculated for subjects with and without the variant and the two rates will be compared using Fisher's exact test. Analysis will be grouped by HCV genotype/subtype and DAA target (NS3 or NS5A). The analysis will include the number of subjects within each genotype/subtype with variants in NS3 only, NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, and any in NS3 + NS5A.

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

- Variants at signature amino acid positions (vs no variant at that position), using detection thresholds of both 2% and 15%. The analysis will include the number of subjects with variants in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, and any in NS3 + NS5A.
- Variants at each non-signature amino acid position at a detection threshold of 15%.
- Each variant at signature amino acid position (vs not that variant) using detection thresholds of 2% and 15%. The analysis will include the number of subjects with variants in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, and any in NS3 + NS5A.

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, and 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. The following tables will be provided (mITT-GT-VF):

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

Analysis 4: (will be available in the primary CSR and will be updated in the final CSR for the study):

The following analyses will be performed for subjects who do not achieve SVR_{12} (with separate summaries for subjects in PVF and non-PVF populations) and have post-baseline resistance data available:

- Listings by subject of all *treatment-emergent variants* relative to the baseline amino acid sequences will be provided for each DAA target (NS3/4A and NS5A).
- Listings by subject of all *variants at signature amino acid positions* in a post-baseline time point for each DAA target (NS3and NS5A).
- The persistence of post-baseline variants at signature resistance-associated amino acid positions for each target (NS3 and NS5A) from subjects will be assessed at Post-Treatment Week 24. Listings by subject and time point of all treatment-emergent variants will be provided for each DAA target (NS3 and NS5A).

HCV Genotype/Subtype

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

Subjects' HCV genotype and subtype may be assessed based on the Inno-LiPA 2.0 Assay used by the Central lab (Covance), the HCV genotype determination by Sanger sequencing a region of NS5B by the Central lab (Covance) and/or from phylogenetic analysis of the full length NS3/4A, and/or NS5A sequences performed by AbbVie. If the

phylogenetic analysis is available, then it will be used to determine the subject's HCV genotype and subtype. If it is not available, then the Sanger sequencing assay result will be used to determine the subject's HCV genotype and subtype, if available. Finally, if neither the phylogenetic analysis result nor the Sanger sequencing assay results is available, then the Inno-LIPA assay results will be used to categorize the subject. This subtype information will be presented in summaries of efficacy subgroup analyses. The baseline characteristic summary will use the results from the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]).

A summary of HCV subtype as provided by the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]) versus phylogenetic analysis also will be provided.

10.8.1.1.1 Presence of Baseline Resistance-Associated Variants

For the efficacy subgroup analyses defined in Section 10.6, any NS3/4A variant and any NS5A variant are defined as follows, where baseline resistance-associated variants based on ≥ 15% NGS detection threshold are considered. Signature amino acid positions of NS3/4A and NS5A by HCV genotype are listed in Table 11.

Table 11. Resistance-Associated Variants by DAA Target and HCV Genotype

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

For example, according to Table 11, all subjects with any baseline variant at amino acid positions 155, 156, or 168 will be counted as having any NS3/4A variant at baseline; any HCV genotype 2 subjects with any baseline variant at amino acid positions 24, 28, 30, 92, or 93 will be counted as having any NS5A variant at baseline.

The number and percent of subjects in the mITT-GT-VF population will be summarized for the presence of baseline resistance-associated variants of:

1. Any NS3/4A variant at baseline (yes/no);
2. Any NS5A variant at baseline (yes/no);
3. Any NS3/4A variant at baseline **or** any NS5A variant at baseline (yes/no);
4. Both NS3/4A and NS5A variant at baseline (i.e., any NS3/4A variant at baseline **and** any NS5A variant at baseline) (yes/no);
5. Presence or absence of any variant
    - 5a. Any NS3/4A variant at baseline only (i.e., without baseline NS5A variants);
    - 5b. Any NS5A variant at baseline only (i.e., without baseline NS3/4A variants);
    - 5c. Both NS3/4A and NS4A variant at baseline;
    - 5d. None (i.e., no baseline variant in either NS3/4A or in NS5A at baseline).

10.8.1.2 HIV Drug-Resistance Analyses

If a subject develops a confirmed, plasma HIV-1 RNA level ≥ 500 copies/mL after starting the study, the subject's HIV-1 PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays. The number of subjects who demonstrate HIV genotypic resistance and the genotypic resistant mutations detected in the samples obtained from these subjects will be tabulated and summarized. Resistance will be defined as described by the IAS-USA Panel.[7]

10.9 Patient Reported Outcomes

The following instruments will be used to collect patient reported outcomes (PROs): SF-36 version 2 (SF-36v2), Fatigue Severity Scale (FSS), and EuroQol-5 Dimensions-3 Level (EQ-5D-3L).

Subject's responses to the EQ-5D-3L will be combined into a unique health state using a 5-digit code with 1 digit from each of the 5 dimensions. The EQ-5D-3L states will be converted into a single preference-weighted health utility index score by applying weights.[4,5] The VAS score will be analyzed separately.

The SF-36v2 measures dimensions of a patient's functional health and well-being in 8 domains and also provides 2 summary scores that characterize a patient's mental (Mental Component Summary; MCS) and physical (Physical Component Summary; PCS) health status. Imputation will be applied to each domain as described in Section 6.3. The score for each of the 8 domains ranges from 0 to 100 and will be normalized according to the user manual.[6] The standardization of the normalized scores will provide the norm-based scores with a mean of 50 and a SD of 10. The two summary scores are based on the norm-based scores. Per the SF-36v2 instrument manual, score for any item with multiple responses will be set to "missing." Subject's responses to the SF-36v2 will be summarized for the PCS and MCS measures and eight individual domain measures.

The FSS measures the impact of fatigue over the past week on specific types of functioning. The survey consists of 9 questions using a 7-point Likert scale. A total score is calculated as the average of the individual item responses (adding up all the answers and dividing by nine). Higher FSS scores indicate a higher degree of impact of fatigue. Imputation will be applied to the total score as described in Section 6.3.

Summary statistics (n, mean) at each visit and for change from baseline (n, mean, SD, minimum, and maximum) to each visit will be provided for the SF-36v2 (MCS and PCS) scores; FSS total score; and EQ-5D-3L health index score and VAS score and will be summarized descriptively at each visit and for change from baseline to each 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 time point of greater than or equal to 2.5 points in the SF-36 MCS and PCS, along with two-sided 95% Normal CI;
- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable time point of greater than or equal to 5 points in the SF-36 domain scores, along with two-sided 95% Normal CI;
- Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable time point of greater than or equal to 0.7 in the FSS total score, along with two-sided 95% Normal CI.

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.

11.2 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.

11.2.1 Treatment-Emergent Adverse Events

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).

11.2.2 Tabulations of Treatment-Emergent Adverse Events

The number and percentage of subjects in each arm and overall 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 for each treatment arm and overall 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 by treatment arm and overall:

- 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 created for each treatment arm.

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 across the 2 treatment arms. 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 event.

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 level of each preferred term. 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.

AIDS-Associated Opportunistic Infections Adverse Events

The number and percentage of subjects experiencing treatment-emergent Opportunistic Infections (OIs) will be tabulated according to SOC and PT for each treatment group and overall. Subjects reporting more than one OI for a given PT will be counted only once for that term. Subjects reporting more than one OI within a SOC will be counted only once for that SOC. Subjects reporting more than one OI will be counted only once in the overall total.

11.2.3 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.

11.3 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.

11.3.1 Variables and Criteria Defining Abnormality

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

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, cholesterol, total protein, glucose, triglycerides, albumin, chloride, bicarbonate, magnesium, total insulin, gamma-glutamyl transferase (GGT), creatinine clearance (calculated using Cockcroft-Gault), and estimated glomerular filtration rate (eGFR) calculated using the modification of diet in renal disease (MDRD) equation defined below.

Urinalysis variables include: specific gravity, ketones, pH, protein, blood, glucose, urobilinogen, bilirubin, leukocyte esterase, and microscopic (reflexly performed if other variables are abnormal).

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

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

The central lab 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].

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 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 for each treatment arm and overall. 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 12 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 for each treatment arm and overall. The post-baseline value must be in a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value in order to be counted. The summary will also include the number and percentage of subjects with a maximum of at least Grade 3 for all laboratory parameters in Table 12. A listing of all relevant laboratory parameters will be provided for each subject who had an increase to Grade 2 or higher for all laboratory variables in Table 12.

Table 12. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
AST	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Alkaline Phosphatase	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
GGT	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Total Bilirubin	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN
Hemoglobin	< LLN – 100 g/L	< 100 – 80 g/L	< 80 g/L	--
White blood cells	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Absolute Neutrophil Count	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
Platelet count	< LLN – 75.0 × 10^9/L	< 75.0 – 50.0 × 10^9/L	< 50.0 – 25.0 × 10^9/L	< 25.0 × 10^9/L
INR	> 1 – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	--
Glucose (increased)	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L	> 27.8 mmol/L
Glucose (decreased)	< LLN – 3.0 mmol/L	< 3.0 – 2.2 mmol/L	< 2.2 – 1.7 mmol/L	< 1.7 mmol/L
Creatinine	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 6 × ULN	> 6 × ULN
Creatinine clearance	< LLN – 60 mL/min	< 60 – 30 mL/min	< 30 – 15 mL/min	< 15 mL/min
Cholesterol	> ULN – 7.75 mmol/L	> 7.75 – 10.34 mmol/L	> 10.34 – 12.92 mmol/L	> 12.92 mmol/L
Albumin	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	--

Assessment of Hepatotoxicity

The number and percentage of subjects in each treatment arm 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 maximum ratio relative to the ULN will be used to determine if subjects meet the criteria listed above. The ALT and total bilirubin values do not need to be concurrent in order to meet the defined criteria. 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).

A listing 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 any of the potential hepatotoxicity criteria defined above. The listings will be reviewed to assess bilirubin (e.g., mixed or direct predominance) and temporal relationships for subjects with ALT $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ 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 $> 5 \times$ ULN and $\geq 2 \times$ baseline;
- AST $> 5 \times$ ULN and $\geq 2 \times$ baseline;
- Total bilirubin $\geq 2.0 \times$ ULN and > baseline.

As noted above, a post-baseline value must be more extreme than the baseline value to be considered. A separate listing will be provided that presents all lab values for the subjects meeting any of these criteria during treatment.

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 vital sign findings are presented in Table 13.

Table 13. Criteria for Potentially Clinically Significant Vital Sign Values

Test/Measurement	Very Low (VL)	Very High (VH)
Systolic Blood Pressure	≤ 90 mmHg AND A decrease of ≥ 20 mmHg from baseline	≥ 180 mmHg AND An increase of ≥ 20 mmHg from baseline
Diastolic Blood Pressure	≤ 50 mmHg AND A decrease of ≥ 15 mmHg from baseline	≥ 105 mmHg AND An increase of ≥ 15 mmHg from baseline
Pulse Rate	≤ 50 bpm AND A decrease of ≥ 15 bpm from baseline	≥ 120 bpm AND An increase of ≥ 15 bpm from baseline
Weight	A decrease of ≥ 15% from baseline	An increase of ≥ 15% from baseline
Body Temperature		> 38.3°C AND An increase of ≥ 1.1°C from baseline

11.4.2 Statistical Methods

The baseline value for vital signs will be the last measurement on or before the day of the first dose of study drug. The same baseline value will be used for change to 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 for each treatment arm. 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 13) will be summarized for each treatment arm. 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 HIV-1 RNA and Flow Cytometry

Plasma HIV-1 RNA will be measured by the central laboratory using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0. For specimens with HIV-1 RNA results that are detectable but not quantifiable, the results are reported as "< 20 CP/ML HIV-1 RNA DETECTED;" for specimens with no HIV RNA detected, the results are reported as: "NO HIV-1 RNA DETECTED."

The analyses of plasma HIV-1 RNA will be conducted only on those subjects who are on stable ART. The analyses for flow cytometry will be conducted on the full safety population.

The following additional safety data will be summarized and analyzed for each treatment arm and overall:

- The percentage of subjects with plasma HIV-1 RNA suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm;
- The number and percentage of subjects with plasma HIV-1 RNA < 20 copies/mL at each applicable time point;
- Change from baseline in CD4+ T-cell count (absolute and percent) to each applicable post-baseline time point;
- Change from baseline in lymphocytes (count) and CD8+ T-cell counts (absolute and percentage) to each applicable post-baseline time point;
- The listing of subjects with a plasma HIV-1 RNA value ≥ 200 copies/mL at any baseline or post-baseline visit during the study.
- The listing of subjects with HIV-1 RNA ≥ 200 copies/mL at any two consecutive baseline or post-baseline visits or with HIV-1 RNA ≥ 500 copies/mL at any one baseline or post-baseline visit during the study.
- The listing of subjects with HIV-1 RNA value ≥ 20 copies/mL and < 200 copies/mL at any baseline or post-baseline visit during the study.

The analysis of change from baseline in CD4+ T-cell count (absolute and percent), lymphocytes (count) and CD8+ T-cell counts (absolute and percent) will report the mean

and median values at baseline and at each applicable post-baseline visit, as well as N, mean, median, standard deviation (SD), minimum and maximum values for the change from baseline within each treatment arm and overall.

Time windows for HIV-1 RNA endpoints to be analyzed using the FDA snapshot algorithm are described as follows.

- The time window for HIV virologic outcomes at the end of treatment is the HIV Week 8 window (Treatment Day 43 to 70) for Arm A and Week 12 window (Treatment Day 71 – 98) for Arm B as described in Table 3.
- The time window for HIV virologic outcomes at Post-Treatment Week 12 is the HIV Post-Treatment Week 12 window (Post-Treatment Day 57 – 999) as described in Table 4.

The subject's HIV virologic outcomes at the end of treatment will be determined per the FDA Snapshot Algorithm in the order below. Vital signs visit dates will be used to determine a subject's study duration.

1. **HIV virologic failure at EOT** = HIV-1 RNA value ≥ 40 copies/mL at the end of treatment; or if the subject discontinues study drug due to HIV virologic failure with the last HIV-1 RNA value prior to study drug discontinuation ≥ 40 copies/mL; or if the subject discontinues study for reason(s) other than AE or death on or before the upper bound of the end of treatment window (Day 70 for Arm A and Day 98 for Arm B) with the last HIV-1 RNA value prior to study discontinuation ≥ 40 copies/mL.
2. **HIV-1 RNA suppression (or HIV virologic success) at EOT** = HIV-1 RNA value < 40 copies/mL at the end of treatment.
3. **No HIV virologic data at EOT** is defined by subcategories as follows:
   - **Discontinued study due to AE or death** if the subject prematurely discontinues study due to AE or death on or before the upper bound of the end of treatment window and has no HIV-1 RNA value in that window; or

- **Discontinued study due to other reason** if the subject prematurely discontinues study due to reason(s) other than AE or death on or before the upper bound of the end of treatment window and has no HIV-1 RNA value in that window; or
- **Missing data during window but on study** if the subject has not discontinued from study on or before the upper bound of the end of treatment window and has no HIV-1 RNA value in that window.

The subject's HIV virologic response at Post-Treatment Week 12 will be determined per the FDA Snapshot Algorithm in the order below. Vital signs visit dates will be used to determine a subject's study duration.

1. **HIV virologic failure at PTW12** = HIV-1 RNA value ≥ 40 copies/mL in the HIV Post-Treatment Week 12 window, or if the subject discontinues study drug due to HIV virologic failure with the last HIV-1 RNA value prior to study drug discontinuation ≥ 40 copies/mL; or if the subject discontinues study for reason(s) other than AE or death on or before the upper bound of the HIV Post-Treatment Week 12 window (Post-Treatment Day 126) with the last HIV-1 RNA value prior to study discontinuation ≥ 40 copies/mL.
2. **HIV-1 RNA suppression (or HIV virologic success) at PTW12** = HIV-1 RNA value < 40 copies/mL in the HIV Post-Treatment Week 12 window.
3. **No HIV virologic data at PTW12** is defined by subcategories as follows:
   - **Discontinued study due to AE or death** if the subject prematurely discontinues study due to AE or death on or before the upper bound of the HIV PTW12 window and has no HIV-1 RNA value in that window; or
   - **Discontinued study due to other reason** if the subject prematurely discontinues study due to reason(s) other than AE or death on or before the upper bound of HIV Post-Treatment Week 12 window and has no HIV-1 RNA value in that window; or

- **Missing data during window but on study** if the subject has not discontinued from study on or before the upper bound of the HIV Post-Treatment Week 12 window and has no HIV-1 RNA value in that window.

12.0 Summary of Changes

12.1 Summary of Changes Between the Latest Version of the Protocol and SAP Version 1.0

1. Updates were made to the resistance analysis plan to be consistent across the HCV glecaprevir/pibrentasvir program.
2. Updates were made to the subgroup efficacy analysis section to be consistent across the HCV glecaprevir/pibrentasvir program

12.2 Summary of Changes Between SAP Version 1.0 and SAP Version 2.0

1. In Section 10.6, "baseline fibrosis stage" was changed to "cirrhosis status."
2. In Section 10.7, "Arm A" was removed from the analysis of the difference of the percentage of subjects achieving SVR_{12} in the ITT population from the historical rate of 96% so that this analysis now includes the entire ITT population.

13.0 References

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Document Approval

Study M14730 - Statistical Analysis Plan Version 2 - 14Dec2016 (E3 16.1.9)

Version: 1.0 **Date:** 15-Dec-2016 04:04:51 PM **Company ID:** 12152016-00F9F6813F6C4B-00001-en

Signed by:	Date:	Meaning Of Signature:
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