1.0 Title Page

Statistical Analysis Plan

Study M16-123

An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects with Genotypes 1 – 6 Chronic Hepatitis C Virus (HCV) Infection

Date: 24 Jan 2018

Version 1.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the AbbVie Statistics and Statistical Programming Departments, or designee, for Study M16-123.

Study M16-123 assesses the pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir (GLE/PIB) in pediatric subjects with chronic hepatitis C virus (HCV) genotypes 1 – 6 chronic Infection with or without compensated cirrhosis and with or without HIV infection, who are HCV treatment-naïve or interferon/pegylated interferon (IFN), ribavirin (RBV) and/or sofosbuvir (SOF) treatment-experienced subjects.

This SAP (Version 1.0) provides details to further elaborate the statistical methods outlined in Clinical Study Protocol M16-123 Amendment 1 dated 25 July 2017, and describes analysis conventions to guide the statistical programming. Analyses will be performed using SAS® Version 9.4 (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 assess the pharmacokinetics (PK) of GLE/PIB by the steady state AUC in pediatric subjects following multiple dosing by age group, and evaluate the safety and tolerability of GLE/PIB by age group, cirrhosis status and across all subjects.

The evaluation of the percentage of subjects with sustained virologic response for 12 weeks post treatment (SVR_{12}) in HCV GT1 – 6 infected pediatric subjects is a part of the primary objectives for the US FDA. For all other countries outside of the US, this assessment is a part of the secondary objectives.

The secondary objectives are to assess C_{max} and clearance of GLE and PIB, the percentages of subjects with on-treatment HCV virologic failure summarized for each age group and overall, the percentages of subjects with post-treatment HCV relapse summarized for each age group and overall, the percentages of subjects with new HCV infection (or re-infection) summarized for each age group and overall, the emergence/persistence of viral variants in subjects with available samples, and palatability of the pediatric formulation.

The growth and development outcomes and patient reported outcomes will also be assessed for the glecaprevir/pibrentasvir treatment regimen in the pediatric subjects.

4.2 Design Diagram

This is a Phase 2/3, multicenter, open-label study to evaluate the PK, safety, and efficacy of GLE/PIB for 8, 12, or 16 weeks in HCV GT1 – 6 infected pediatric subjects ≥ 3 to < 18 years of age, who are either treatment-naïve, treatment-experienced to IFN with or without RBV or treatment-experienced to SOF with IFN and/or RBV. Subjects may be non-cirrhotic or have compensated (Child-Pugh A) cirrhosis. Subjects with HCV/HIV-1 co-infection are eligible for study inclusion.

The study will enroll approximately 110 HCV-infected pediatric subjects, divided into four age groups, 3 to < 6, 6 to < 9, 9 to < 12, and 12 to < 18 years of age. Enrollment will begin in the age group 12 to < 18 years old among subjects who are willing to swallow the adult formulation of GLE/PIB (Part 1). Part 2 of the study will enroll the remaining age groups; those will receive the pediatric formulation of GLE/PIB.

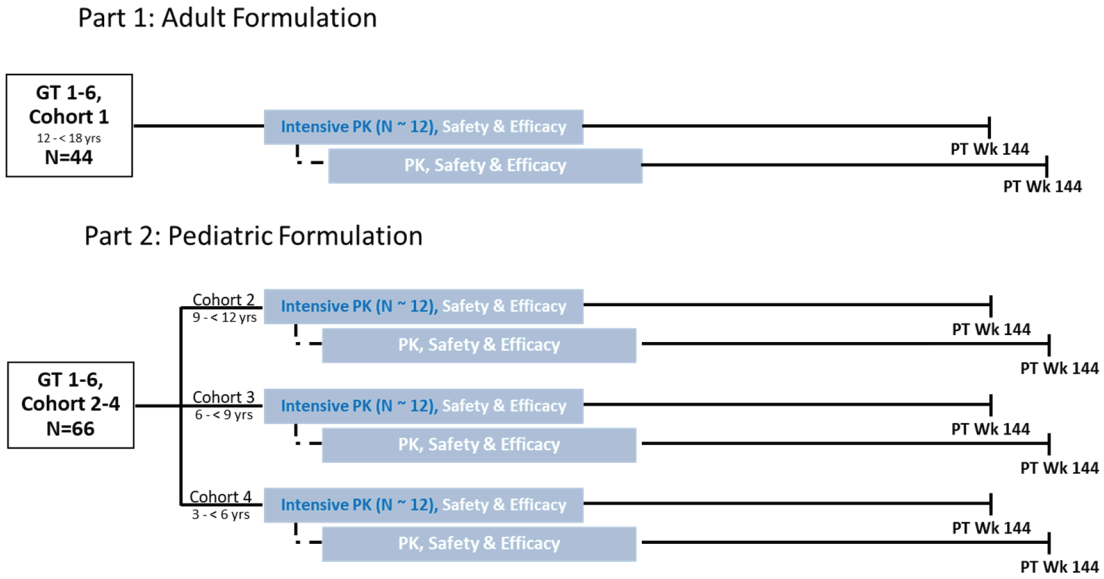
Within each age group, approximately 12 HCV-infected pediatric subjects will be enrolled for intensive pharmacokinetics (IPK) in order to adequately characterize the PK of a particular age group for dose confirmation, and the remainder of subjects will be enrolled for the evaluation of safety and efficacy of each age group until the total pediatric study population reaches approximately 110 subjects. Additional PK assessments will be obtained for subjects enrolled in Japan for the purpose of further characterization within

Japanese subjects; this is not included within the aforementioned 12 subjects per age group.

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

A study schematic is shown below in Figure 1.

Figure 1. Study Design



Eligible subjects will be assigned to a treatment regimen according to their HCV genotype, cirrhosis status and prior HCV treatment experience as shown in Table 1 for global subjects and Table 2 for subjects in Japan. For patients with an indeterminate or mixed genotype, treatment duration will default to the respective GT3 duration based upon treatment-experience and cirrhosis status. The treatment duration for subjects in Japan is consistent with the approved label in Japan.

Table 1. Treatment Regimen and Duration (Excluding Subjects in Japan)

Patient Population	Duration
GT1 – 6 NC, TN GT1, 2, 4 – 6 NC, TE	8 weeks
GT1 – 6 C, TN GT1, 2, 4 – 6 C, TE	12 weeks
GT3 TE	16 weeks

Legend: C = Cirrhotic; NC = Non-Cirrhotic; TE = Treatment experienced to IFN (alpha, beta or pegIFN) ± RBV or SOF/RBV ± pegIFN; TN = Treatment Naïve

Table 2. Treatment Regimen and Duration (Subjects in Japan)

Patient Population	Duration
GT1 – 2 NC, TN, TE – IFN	8 weeks
GT1 – 2 C, TN, TE – IFN GT3 – 6 NC, C, TN, TE – IFN GT1 – 6 TE – SOF	12 weeks

Legend: C = Cirrhotic; NC = Non-Cirrhotic; TE – IFN = Japan Treatment experienced to IFN (alpha, beta or pegIFN) ± RBV; TE – SOF = Japan Treatment experienced to SOF/RBV ± pegIFN; TN = Treatment Naïve

4.3 Sample Size

The proposed sample size of 48 subjects (approximately 12 subjects for each age cohort for IPK sampling with separate from sampling performed in subjects in Japan) is expected to adequately characterize the PK of GLE and PIB to enable dose selection in pediatric subjects.

4.4 Planned Interim Analyses and Final Analysis

All analyses will be conducted by statisticians and programmers at AbbVie or designees according to the methodologies specified in this SAP.

The first interim analysis will occur once all 12 subjects participating in IPK in Part 1 complete PT Week 12 or prematurely discontinue from the study. A second interim analysis will occur once all subjects in Part 1 complete PT Week 12 or prematurely

discontinue from the study. A third interim analysis will occur once all subjects participating in the IPK portion in Part 2 complete PT Week 12 or prematurely discontinue from the study. A fourth interim analysis will occur once all subjects in Parts 1 and 2 complete PT Week 12 or prematurely discontinue the study. Final analysis will occur after the completion of the whole study.

For each planned interim analysis, data will be locked after performing data cleaning. Data after each interim analysis will be added to a new version of the database. The final analysis will be conducted when all subjects enrolled in the study have completed the 144 week post-treatment visit or prematurely discontinued from the study. Data after the last interim 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.

There is no intention of stopping the study early based on efficacy findings from the interim analyses. The intention is to follow all subjects who receive study drug for 144 weeks following treatment.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

If efficacy is determined to be lesser in a dose lower than the final dose, non-safety analyses may be performed with the subjects who receive a dose lower than the final dose chosen for the subject's age group summarized separately.

5.1.1 Intention-to-Treat (ITT) Population

All subjects who receive at least one dose of study drug will be included in the ITT population. Demographic, baseline characteristic, exposure, concomitant medication and medical history analyses will be performed on the ITT population overall and by age group. Efficacy analyses will be performed on the ITT population.

5.1.2 Modified Intention-to-Treat (mITT) Population

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

5.1.3 Safety Population

All subjects who receive at least one dose of study drug will be included in the safety population. Safety analysis will be performed on the safety population overall and by age group.

5.2 Variables Used for Stratification of Randomization

This study is not randomized. Eligible subjects will be assigned to a treatment regimen based on HCV genotype, cirrhotic status, prior HCV treatment experience, and whether the subjects are in Japan or not.

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 1,999.

6.2 Definition of Analysis Windows

For efficacy analyses of HCV RNA and resistance, the time windows specified in Table 3 and Table 4 describe how HCV RNA and resistance data are assigned to protocol-specified time points during the Treatment and PT Periods, respectively. All time points and corresponding time windows are defined based on the date/time of blood sample collection.

For safety laboratory data, vital signs, and growth and development endpoints (except growth rate), the time windows specified in Table 3 and Table 5 describes how data are assigned to protocol specified time points. For the calculation of growth rate only, the time window specified in Table 6 will be used to assign height to a specific visit window before growth rate will be calculated as the change in height over change in age from the previous visit at Post-Treatment Weeks 12, 48, 96, and 144.

For PRO questionnaire, the time windows specified in Table 7 and Table 8 describes how data are assigned to protocol specified time points.

For palatability questionnaire, the time windows specified in Table 9 describes how data are assigned to protocol specified time points during the treatment period.

For longitudinal Fibrotest and APRI, the time windows specified in Table 10 describes how data are assigned to protocol specified time points during the Post-Treatment period.

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, a vital sign parameter, or a growth and development endpoint, the average of the values will be used to calculate descriptive statistics and in analyses of the mean change from baseline.

Table 3. Analysis Time Windows for HCV RNA, Resistance Endpoints, Laboratory, Vital Sign Measurements, Growth and Development Endpoints (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
Week 16[c]	112	99 to 126
Final Treatment Visit[d]	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. For 16-week treatment only.

d. 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
Post-Treatment Week 24	168	127 to 210
Post-Treatment Week 36	252	211 to 294
Post-Treatment Week 48	336	295 to 504
Post-Treatment Week 96	672	505 to 840
Post-Treatment Week 144	1,008	841 to 1,999
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 5. Laboratory Data, Vital Sign Measurements, Growth and Development Endpoints (Except Growth Rate) 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 42
Post-Treatment Week 12	84	71 to 126
Post-Treatment Week 24	168	127 to 210
Post-Treatment Week 36	252	211 to 294
Post-Treatment Week 48	336	295 to 504
Post-Treatment Week 96	672	505 to 840
Post-Treatment Week 144	1,008	841 to 1,999
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 and growth and development endpoints are collected at every PT visit; hematology, chemistry, urinalysis, and coagulation panels are collected at Post-Treatment Week 4 and PTDC (if subject discontinued prior to Post-Treatment Week 4). For subjects with compensated cirrhosis at baseline, chemistry and coagulation panels are collected to calculate the Child Pugh Score.

Table 6. Visit Windows for Growth Rate Calculation (Post-Treatment Period)

Scheduled Time	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Days Range)
Post-Treatment Week 12	84	3 to 210
Post-Treatment Week 48	336	211 to 504
Post-Treatment Week 96	672	505 to 840
Post-Treatment Week 144	1,008	841 to 1,999
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. For the calculation of growth rate only, height will be assigned to a visit as described in the table above, then growth rate will be calculated as the change in height (millimeter) over the change in age (years) from the previous visit. If height is missing at a visit and/or the previous visit, then growth rate will be missing for the visit.

Table 7. Analysis Time Windows for PRO Instruments (Treatment Period)

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Day 1/Baseline[a]	1	≤ 1[a]
Week 8[b]	56	2 to 70
Week 12[c]	84	71 to 98
Week 16[d]	112	99 to 126
Final Treatment Visit[e]	2 to ≤ 2 days after last dose of study drug	

a. Day of first dose of study drug.

b. For 8-week treatment only.

c. For 12-week treatment only.

d. For 16-week treatment only.

e. 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, 12 or 16 depending on treatment assignment.

Table 8. Analysis Time Windows for PRO Instruments (Post-Treatment Period)

Scheduled Time	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Days Range)
Post-Treatment Week 12	84	3 to 1,999
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.

Table 9. Analysis Time Windows for Palatability Questionnaire (Treatment Period Only)

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Week 2	14	2 to 35
Week 8[a]	56	36 to 70
Week 12[b]	84	71 to 98
Week 16[c]	112	99 to 126
Final Treatment Visit[d]	2 to ≤ 2 days after last dose of study drug	

a. For 8-week treatment only.

b. For 12-week treatment only.

c. For 16-week treatment only.

d. 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. Palatability questionnaire are administrated to subjects in Part 2 at Week 2 and End of Treatment Visit or premature discontinuation visit.

Table 10. Analysis Time Windows for Longitudinal Fibrotest and APRI (Post-Treatment Period)

Scheduled Visit	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Day Range)
Post-Treatment Week 12	84	3 to 175
Post-Treatment Week 48	336	176 to 504
Post-Treatment Week 96	672	505 to 840
Post-Treatment Week 144	1,008	841 to 1,999
Final Post-Treatment Visit[a]	> 2 days after the last dose of study drug	

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.

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 PedsQL, 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 dimension will be considered missing.

Regardless of the imputation method described above, if a subject starts another treatment for HCV, then all PRO data for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses.

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

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

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, and body mass index (BMI), BMI z score (BMI z score will be calculated using WHO published BMI-for-age z score tables),[5] weight and height z scores (weight and height z scores will be calculated using WHO published weight-for-age z score and height-for-age z score tables. Categorical demographic variables include sex, race, black race (black or non-black), ethnicity, age category (≥ 3 to < 6 years, ≥ 6 to < 9 years, ≥ 9 to < 12 years, ≥ 12 to < 18 years), birth year, weight category (≥ 12 to < 20 kg, ≥ 20 to < 30 kg, ≥ 30 to < 45 kg, ≥ 45 kg), weight z score category (< –1, –1 to 1, > 1), Height z-score category (< –1, –1 to 1, > 1), BMI z-score category (< –1, –1 to 1, > 1) country, and geographic region (North America, Europe, or Japan).

Weight-for-age reference data are not available beyond age 10 because this indicator does not distinguish between height and body mass in an age period where many children are experiencing the pubertal growth spurt and may appear as having excess weight (by weight-for-age) when in fact they are just tall. Subjects who are older than 10 years at the time of the corresponding weight measurement will be excluded from the summary of weight z score.

When defining geographic region, sites in the United States, Puerto Rico, and Canada will be grouped under North America; sites in Belgium, Germany, Russia, Spain and the United Kingdom will be grouped under Europe; sites in Japan will be grouped together as Japan.

Continuous baseline characteristics include baseline $\log_{10}$ HCV RNA level, creatinine clearance, eGFR, platelet count, albumin, GGT, alpha fetoprotein (for cirrhotic subjects only), Fibrotest, APRI, FIB-4, AST, ALT, total, direct, and indirect bilirubin for all subjects.

Categorical baseline characteristics include:

- HCV genotype and subtype (using central laboratory results and final genotype/subtype results, see Section 10.8);
- 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);
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, or F4);
- Baseline cirrhosis status (cirrhotic or non-cirrhotic)
- Baseline HCV RNA level ($< 1{,}000{,}000 \geq 1{,}000{,}000$ to $< 2{,}000{,}000$, $\geq 2{,}000{,}000$ IU/mL);
- Baseline platelet count (< 90 or $\geq 90 \times 10^9$/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline eGFR (< 30, ≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73 m^2);
- HIV co-infected subjects (yes/no);
- History of bleeding disorders (yes/no);
- History of depression or bipolar disorder (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);
- Nicotine use (user, ex-user, or non-user);
- Alcohol use (drinker, ex-drinker, or non-drinker);
- Concomitant use of Proton Pump Inhibitors (PPIs).
- Concomitant use of Statins (yes/no);

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

- Baseline Child-Pugh score (5, 6, or > 6),
- Baseline alpha fetoprotein (< 20 or ≥ 20 ng/mL),

For treatment experienced subjects, any regimen that contains SOF with or without IFN or RBV is SOF-based. Otherwise, any regimen that contains IFN with or without RBV is IFN-based.

Any concomitant medication coded to the WHO Drug Dictionary ATC code of A02BC will be counted as a PPI. Any concomitant medication coded to the WHO Drug Dictionary ATC code of C10AA or C10BX will be counted as a statin.

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 11.

Table 11. Baseline Fibrosis Stage

Baseline Fibrosis Stage, Metavir Equivalents	Liver Biopsy Metavir, Batts Ludwig, Knodell, IASL, Scheuer, New Inuyama or Laennec Score	Liver Biopsy Ishak Score	FibroScan (kPa)	FibroTest*
F0 – F1	0 or 1	0, 1, or 2	< 8.8	≤ 0.48
F2	2	3	≥ 8.8 to < 9.6	0.49 to 0.58
F3	3	4	≥ 9.6 to < 12.5	0.59 to 0.72
F4	4	≥ 5	≥ 12, 5	≥ 0.73

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

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

Baseline Child-Pugh score is the sum of the points assigned for each of the five observed findings as defined in Table 12.

Table 12. Child-Pugh Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/L (mg/dL)	< 34.2 (< 2)	34.2 – 51.3 (2 – 3)	> 51.3 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 – 35 (2.8 – 3.5)	< 28 (< 2.8)
INR	< 1.7	1.7 – 2.3	> 2.3
Ascites*	None	Slight	Moderate to severe
Hepatic encephalopathy**	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (or refractory)

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

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

Baseline APRI and FIB-4 are 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.

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

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

Histories of bleeding disorders and depression or bipolar disorder will be based on the Medical History (MH) eCRF, as defined in Table 13.

Table 13. Medical/Surgical History eCRF

	Medical History eCRF	
Subgroup	**Body System**	**Condition/Diagnosis**
Bleeding disorders	Blood	Clotting/bleeding problems Factor deficiency Hemophilia Von Willebrand disease
Depression or bipolar disorder	Neurologic and Psychiatric System	Bipolar disorder Depression

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

The number and percentage of subjects taking prior medications, concomitant medications, and post-treatment HCV medications will be summarized by generic drug name based on the WHO Drug Dictionary. The prior HCV medications taken by treatment experienced subjects and collected on the "Last Prior HCV Therapy" and "Second to Last Prior HCV Therapy" eCRFs will be summarized separately from other prior medications, and will not be included in the summary of all prior and concomitant medication.

8.0 Patient Disposition

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

8.1 Disposition of Safety Population

The number of subjects in each of the following categories will be by investigator for each age group 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;
- Subjects ongoing in the Post-Treatment Period (if applicable at the time of analysis).

The number and percentage of subjects who discontinued study drug will be summarized by reason (all reasons) and by primary reason (per eCRF) for each age group 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 age group and overall. Reasons for study drug interruptions will be presented in the CSR listings.

9.0 Study Drug Exposure and Compliance

Exposure and compliance will be summarized on the ITT population by age group and overall.

9.1 Exposure

The duration of exposure to study drug will be summarized by assigned treatment duration for each age group and for all subjects. 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 30 days
- 31 to 60 days
- 61 to 75 days
- 76 to 90 days
- 91 to 105 days
- > 105 days

In addition, the number and percentage of subjects with study drug duration of ≥ 52 days for subjects assigned to 8 weeks, ≥ 77 days for subjects assigned to 12 weeks and ≥ 103 days for subjects assigned to 16 weeks will be summarized by age group and overall.

9.2 Compliance

For the adult formulation, the GLE/PIB tablet, tablet is the dose unit for drug accountability. For the pediatric formulation, bottle/sachet is the dose unit for drug accountability and the return status for each dose unit is recorded as either full/sealed, empty, or unsealed but not empty separately for glecaprevir and pibrentasvir or for glecaprevir and pibrentasvir combined if mixed together. A bottle/sachet is considered to be taken only if the return status is empty.

At each visit (starting with the Week 4 visit) during the Treatment Period, the total number of dose units dispensed and returned is recorded. The compliance for each type of dose unit during the treatment period will be calculated as the percentage of dose units taken relative to the total dose units expected to be taken. The total number of dose units expected to be taken will be equal to the total number of dose units 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 each type of dose unit and summarized separately with the mean, median, standard deviation, minimum, and maximum for each type of dose unit by age group and overall. A listing of compliance for each subject will be provided. The percentage of compliant subjects will be summarized for each study drug by age group and overall, based on data as observed.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

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

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

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

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

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

$Relapse_{12}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug (up to and including the SVR_{12} window) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment 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 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 a study drug duration of 52 days or greater for subjects assigned to 8 weeks of treatment, 77 days or greater for subjects assigned to 12 weeks of treatment, and 103 days or greater for subjects assigned to 16 weeks of treatment. 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 active treatment in a subject who had HCV RNA < LLOQ at Final Treatment Visit, along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis of the NS3 or NS5A, and/or NS5B gene sequences. Reinfection in the case of the same HCV subtype is defined as a clade switch, as indicated by the lack of clustering between the baseline and post-treatment sequences by phylogenetic analysis. If phylogenetic analysis is not possible due to technical difficulties, HCV reinfection may be determined with a confirmed HCV genotype or subgenotype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Post-treatment relapse is defined as described earlier (**Relapse$_{12}$, Relapse$_{24}$, Relapse$_{overall}$**), and no genotype, subtype, or clade switch compared with baseline as determined by phylogenetic analysis of the NS3 or NS5A gene sequences. If phylogenetic analysis is not possible due to technical difficulties, the subject will be defined as having a post-treatment relapse unless an HCV genotype or subtype switch is confirmed by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

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

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

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

2. HCV reinfection (see definition described earlier);
3. $Relapse_{12}$;
4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{12} non-responder who prematurely discontinued study drug [study drug duration < 52 days for subjects assigned to 8 weeks of treatment, < 77 days for subjects assigned to 12 weeks of treatment, and < 103 days for subjects assigned to 16 weeks of treatment] and did not meet the **On-treatment virologic failure or reinfection** definitions);
5. Missing follow-up data in the SVR_{12} window (defined as any subject who completed study drug without data in the SVR_{12} window after applying the imputation rules and not meeting the definitions of [1], [2], [3], or [4]);
6. Other (defined as any SVR_{12} non-responder not meeting the definitions of [1] – [5]).

Reasons for SVR_{24} Non-Response

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

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. HCV reinfection;
3. $Relapse_{12}$
4. $Relapsed_{24}$;
5. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{24} non-responder who prematurely discontinued study drug [study drug duration < 52 days for subjects assigned to 8 weeks of treatment, < 77 days for subjects assigned to 12 weeks of treatment, and < 103 days for subjects assigned to 16 weeks of treatment] and did not meet the **On-treatment virologic failure**, **$Relapse_{12}$**, or **$Relapse_{24}$** definitions);

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

For the reasons for SVR_{12} and SVR_{24} nonresponse defined above, subjects are only to be counted in 1 category. Specifically, subjects who were SVR_{12} or SVR_{24} nonresponders meeting the definition of HCV reinfection will be counted in the reinfection category regardless of whether they meet the definition of prematurely discontinued study drug, $relapse_{12}$ or $relapse_{24}$.

10.2 Handling of Multiplicity

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

10.3 Primary PK and Primary Efficacy Analysis

10.3.1 Primary PK Analysis

The primary pharmacokinetic endpoint will be the steady state AUC of GLE and PIB estimated by non-compartmental pharmacokinetic analysis or population pharmacokinetic analysis. The 95% confidence interval for the geometric mean of AUC values will be calculated. For subjects enrolled in Japan, the pharmacokinetic parameters will be summarized separately.

10.3.2 Primary Efficacy Analysis

For US regulatory agency the efficacy endpoint of SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) across all subjects in the ITT population is considered primary efficacy endpoint. For all other regulatory agencies the SVR_{12} efficacy endpoint is considered secondary.

The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of SVR_{12} non-responders is less than 5, where the Wilson's score method[1] will be used to calculate the confidence interval instead.

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

10.4 Secondary PK and Efficacy Analyses

10.4.1 Secondary PK Analyses

The secondary PK endpoint is:

1. C_{max} and clearance of GLE and PIB

C_{max} and clearance values will be estimated by non-compartmental pharmacokinetic analysis or population pharmacokinetic analysis. For subjects enrolled in Japan, the pharmacokinetic parameters will be summarized separately.

10.4.2 Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment HCV virologic failure (defined as **On-treatment virologic failure**) by age group and overall,
- The percentage of subjects with post-treatment HCV relapse (defined as **$Relapse_{12}$**; subjects with reinfection will be summarized separately) by age group and overall,
- The percentage of subjects with re-infection by age group and overall,
- Assessment of palatability of the pediatric formulation by age group and overall.

The number and percentage of subjects with on-treatment virologic failure, post-treatment relapse (**$Relapse_{12}$**) and re-infection will be summarized along with two-sided 95% confidence interval using Wilson's score method.

For the assessment of palatability, the number and percentage of subjects with each categorical answer marked will be presented for each question in the palatability questionnaire at each applicable treatment visit by age group and overall. A listing of acceptability questionnaire results and comments for each applicable subject over applicable treatment visits will be produced.

10.5 Sensitivity Analysis for SVR

As sensitivity analysis, the number and percentage of subjects in the mITT-VF population achieving SVR_{12}, as applicable, will be summarized, along with a two-sided 95% confidence interval using Wilson's score method.

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 if that was not used in the primary analysis.

A listings of subject excluded from the mITT-VF population will be provided.

10.6 Efficacy Subgroup Analysis

The percentage of subjects with SVR_{12} in the ITT population will be calculated along with the corresponding 2-sided 95% Wilson score confidence interval for the following subgroups if applicable:

- HCV genotype (1, 2, 3, 4, 5, or 6);
- Prior HCV treatment history (treatment-naïve or treatment-experienced);
- For treatment-experienced subjects, type of previous regimen (IFN- or SOF-based);
- Sex (male or female);
- Race (black or non-black);

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Geographic region (North America, Europe, Japan);
- Height z-score (< –1, –1 to 1 or > 1);
- BMI z-score (< –1, –1 to 1 or > 1);
- Drug compliance (< 80% versus ≥ 80%)
- Baseline fibrosis stage (F0 – F1, F2, F3 or F4);
- Cirrhosis status (yes/no);
- Baseline HCV RNA level (< 1,000,000, ≥ 1,000,000 to < 2,000,000, ≥ 2,000,000 IU/mL);
- Baseline platelet count (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no);
- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no).
- Concomitant use of Statins (yes/no);

For subjects with cirrhosis only:

- Baseline Child-Pugh Score (5, 6, or > 6).
- Baseline platelets (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);

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) by age group and overall;
- The percentage of subjects with SVR_{12} by age group;
- The percentage of subjects with SVR_4 by age group and overall;

- The percentage of subjects with SVR_{24} by age group and overall;

All rates will be presented with two-sided 95% confidence intervals using the Wilson's score method.

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 HCV RNA value of those indicating the occurrence of relapse. A similar listing will be prepared for subjects who prematurely discontinued treatment and relapsed after having HCV RNA < LLOQ at their Final Treatment Visit. A listing of subjects in the ITT population excluded from the relapse denominator (e.g., study drug duration < 52 days for subjects assigned to 8 weeks of treatment) will be provided, as applicable.

The number and percentage of subjects who do not achieve SVR_{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_{24} out of all subjects who achieved SVR_{12}. The NPV of SVR_{12} on SVR_{24} is the proportion of subjects who do not achieve SVR_{24} out of all subjects who did not achieve SVR_{12}. Similarly, the concordance between SVR_4 and SVR_{12} will be summarized.

10.8 Resistance Analyses

10.8.1 HCV Drug-Resistance Analyses

Full length NS3/4A or NS5A from all available 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 available 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, signature amino acid positions and a key subset of amino acid positions are listed in Table 14. Appropriate subtype-specific prototypic reference sequence will be used for comparison with sequences from samples.

Table 14. 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, 1 – other (non 1a/1b)	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, 1 – other (non 1a/1b)	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 polymorphism: a polymorphism by NGS in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on 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 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 cohort by HCV genotype/subtype within each listing.

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

- A listing of all baseline polymorphisms (2% detection threshold) at signature amino acid positions for each DAA target (NS3 and NS5A) (ITT).
- The number and percentage of subjects with baseline polymorphisms at detection-thresholds of 2% and 15% at signature amino acid positions (ITT). This table includes prevalence of each baseline polymorphism, and a summary of the number of subjects with polymorphisms in NS3 only, NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, and any in NS3 + NS5A.
- Total number and percentage of subjects with baseline polymorphisms ***at the 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 the 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: Analysis 2 will be applicable to Cohort 1 only. The impact of baseline polymorphisms on treatment outcome will be assessed for the **mITT-VF** population as follows: for each polymorphism, the SVR_{12} rate will be calculated for subjects with and without the polymorphism and the two rates will be compared using Fisher's exact test. Analysis will be grouped by HCV genotype/subtype 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 polymorphisms on treatment outcome:

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

Analysis 3: Analysis 3 will be applicable to Cohort 1 only. In subjects with or without baseline 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-VF):

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

Analysis 4:

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 (NS3 and NS5A).
- The persistence of post-baseline variants at signature resistance-associated amino acid positions for each target (NS3 and NS5A) from subjects will be assessed at Post-Treatment Week 24. Listings by subject and time point of all treatment-emergent variants will be provided for each DAA target (NS3 and NS5A).

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV sequence from baseline samples for all subjects in Part 1, and from subjects with available sample in Part 2 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 used in summaries of efficacy subgroup analyses. The baseline characteristic summary will use the results from the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]).

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

10.9 Growth and Development

The following growth and development endpoints will be calculated in the ITT population.

- Growth rate at Post-Treatment Weeks 12, 48, 96 and 144 (defined as change in height over change in age from the previous visit)
- Weight z score[5]
- Height z score[5]
- Body mass index (BMI) z score[5]

Weight, height, and BMI z scores will be calculated using WHO published weight-for-age z score, height-for-age z score, and BMI-for-age z score tables, respectively. As described in Section 7.1, subjects who are older than 10 years at the time of the corresponding weight measurement will be excluded from the analyses of weight z score. If a subject becomes older than 19 years during the study, the WHO standards at 19 years old will be used to calculate height z score and BMI z score after 19 years old as these WHO standards are very close to the adult standards.

Growth rate will be summarized with N, mean and SD together, median and range together at each applicable post baseline visit by gender for all and for age group separately. Weight, height and BMI z scores will be summarized with N, mean and SD together, median and range together at each applicable post baseline visit for all and by age group.

10.10 Patient Reported Outcomes

The patient reported outcomes data will be analyzed in the ITT population.

At Baseline, End of Treatment, and Post-Treatment Premature Discontinuation, subjects will complete the PRO instrument, PedsQL, with the assistance of a parent/guardian (where allowed per local regulatory guidelines). The PedsQL Generic Core Scales is a 23 item questionnaire designed to measure the core dimension of health as defined by the

World Health Organization (WHO) along with role (school) functioning. The PedsQL consists of 4 Multidimensional Scales (Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning) and 3 Summary Scores (Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score). Subjects who are older than 5-years of age and are able to read and understand the questions should complete the questionnaire by themselves. For subjects who are 5-years of age or younger or who are not comfortable with reading the questions, their parent(s)/guardian(s) should complete the parent/guardian proxy-report.

Across subjects enrolled in Part 1 and 2 (based on ITT population), summary statistics of change from baseline to Week 8 (only applicable to subjects assigned to 8 weeks of treatment), Week 12 (only applicable to subjects assigned to 12 weeks of treatment), Week 16 (only applicable to subjects assigned to 16 weeks of treatment) and Final Treatment Visit and Final PT Visit (n, mean, SD, minimum and maximum) of 3 summary scale scores will be provided by age group and overall. In addition the same summaries will be created separately for subjects who complete all the questionnaires by themselves and for subjects whose parent(s)/guardian(s) always complete the parent/guardian proxy-report.

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 overall and by age group.

11.2 Analysis of Adverse Events

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

HIV co-infected subjects are allowed to enroll into the study and the AIDS-associated opportunity infections will be flagged on the AE eCRF and in the AE database, which be excluded from all AE summary tables and listings. A separate listing of AIDS-associated opportunity infections will be generated for the HIV co-infected subjects if there are HIV co-infected subjects enrolled under such conditions.

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any adverse event 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 age group and overall with treatment-emergent AEs will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The SOC will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

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

Adverse Event Overview

An overview of AEs will be presented for each age group 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 AE;
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Treatment-emergent AEs of grade 3 or higher;
- Treatment-emergent adverse events of Grade 3 or higher with a "reasonable possibility" of being related to DAA (glecaprevir/pibrentasvir);
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Treatment-emergent AEs leading to discontinuation of study drug;
- DAA-related treatment-emergent AEs leading to discontinuation of study drug;
- Serious treatment-emergent AEs leading to discontinuation of study drug;
- Treatment-emergent AEs leading to interruption of study drug;
- Treatment-emergent AEs leading to death;
- Deaths.

Adverse Events by SOC and PT

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

- Treatment-emergent adverse events;
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (glecaprevir/pibrentasvir);
- Treatment-emergent AEs of Grade 3 or higher;

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

A listing of treatment-emergent AEs grouped by body system and preferred term with subject numbers will be created for each age group.

Adverse Events by PT

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

Adverse Events by Maximum Severity Grade Level

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

Adverse Event by Maximum Relationship

Treatment-emergent AEs also will be summarized by maximum relationship of each PT to study drug (DAA), as assessed by the investigator. If a subject has an AE with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

11.2.3 Adverse Events of Special Interest

Adverse events of special interest included the following:

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

For the hepatic decompensation/hepatic failure AE of special interest, the number and percentage of subjects experiencing at least one treatment-emergent AE in the search will be presented by SOC and preferred term and across all SOCs/preferred terms. In addition, a by-subject listing of treatment-emergent AEs meeting the search criterion will be provided.

For the hepatocellular carcinoma AE of special interest, the number and percentage of subjects experiencing at least one post-baseline AE in the search will be presented by SOC and preferred term and across all SOCs/preferred terms. In addition, a by-subject listing of all post-baseline (i.e., including both treatment-emergent and non-treatment emergent) AEs meeting the search criterion will be provided.

11.2.4 Listing of Adverse Events

The following listings of AEs will be prepared:

- All serious AEs (from the time the subject signed the study-specific informed consent through the end of the study),
- Treatment-emergent serious AEs,
- Treatment-emergent AEs leading to death,
- Treatment-emergent AEs leading to discontinuation of study drug,
- Treatment-emergent AEs leading to study drug interruption.
- Treatment-emergent AEs in each of the AEs of special interest categories.

11.3 Analysis of Laboratory Data

Data collected from the central and local laboratories, including additional laboratory testing due to 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, total protein, glucose, albumin, chloride, bicarbonate, magnesium, , gamma-glutamyl transferase (GGT), alpha fetoprotein, fibrotest, APRI, creatinine clearance (calculated using Cockcroft-Gault), and glomerular filtration rate (GFR) for creatinine adjusted for boday surface area (BSA).

Urinalysis variables include: specific gravity and pH.

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].

The central lab calculates the GFR for creatinine adjusted for BSA based on the following formula:

GFR for serum adjusted for BSA (mL/min/1.73 m^2) = CrCl (mL/min) × 1.73/ {[(weight in kg) × (height in meter)]$^{0.5}$/60}.

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 age group 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 15 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 age group and overall. To be counted, the post-baseline value must have a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value. 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 15. 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 15.

Table 15. 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 Hepatic Laboratory Values

The number and percentage of subjects in each age group and overall meeting the following criteria during treatment will be summarized:

- Post nadir (preceding value is lower than the subsequent value) ALT > 5 × ULN (regardless of grade change);
- Total bilirubin ≥ 2 × ULN and > baseline (i.e., a post-baseline value must be more extreme than the baseline value to be considered)
- Post nadir ALT > 3 × ULN and total bilirubin > 2 × ULN (Hy's law quadrant)

- Post nadir ALT > 3 × ULN and total bilirubin ≤ 2 × ULN (Temple's corollary quadrant)

Four listings (one for each bullet above) of all liver function tests including ALT, AST, total, indirect and direct bilirubin, ratio of direct to total bilirubin, and alkaline phosphatase values will be provided for each subject who met the criterion defined above.

Hepatic Laboratory Abnormalities of Interest

Among the labs assessed under "Assessment of Hepatic Laboratory Values" the following criteria are of interest:

- Confirmed post-nadir ALT > 5 × ULN;
- Post nadir ALT > 3 × ULN and a concurrent total bilirubin > 2 × ULN with direct bilirubin/total bilirubin ratio > 0.4

Two listings (one for each bullet) of all liver function tests including ALT, AST, total, indirect and direct bilirubin, ratio of direct to total bilirubin, and alkaline phosphatase values will be provided for each subject who met the criterion defined above.

For the **assessments of hepatic laboratory values** and **hepatic laboratory abnormalities of potential interest**, the maximum ratio relative to the ULN will be used to determine if subjects meet any of the criteria listed above. The ALT and total bilirubin values do not need to be concurrent in order to meet the defined criteria in statistical summaries. For ALT, the post-baseline value must represent an increase from the first nadir (including baseline) to be counted. First nadir is defined as the last value prior to the first increase. For total bilirubin, a subject will be counted if the post-baseline laboratory value meets the above criteria regardless of the baseline laboratory value (i.e., the post-baseline laboratory value does not need to be worse than the baseline laboratory value), except where noted above. A confirmed post-nadir increase in ALT is defined as two consecutive values of ALT > 5 × ULN after nadir, either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement. A single post-nadir ALT value of greater than 5 × ULN followed by lost to

follow-up (no additional ALT values) also will be considered (i.e., will not require confirmation). The ratio of direct to total bilirubin will be calculated using the same date/time sample corresponding to the total bilirubin elevation.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

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

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.

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

12.0 Summary of Changes

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

1. The protocol stated to use Safety Population for Demog/baseline outputs; SAP changed these analyses to be run on ITT to align with the new HCV SAP template.
2. Protocol Section 8.1.6.2 planned shift tables for clinical laboratory values from low/normal to high and high/normal to low; SAP removed these analyses as the reference ranges won't work for the pediatric population.

3. Protocol Section 8.1.6.3 planned summary table for vital signs meeting Potentially Clinically Significant criteria; SAP removed these analyses due to the criteria are not applicable to pediatric population.
4. Protocol Section 8.1.3 planned change from baseline summary statistics for height, weight, and BMI z scores; SAP removed these analyses as the summary of the z scores at each applicable visit is sufficient.
5. Updates were made to the subgroup efficacy analysis section to be consistent across the HCV glecaprevir/pibrentasvir program.

13.0 References

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4. Johnson VA, Calvez V, Huldrych GF, et al. Update of the drug resistance mutations in HIV-1: March 2013. Top Antivir Med. 2013;21(1):4-12.
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