1.0 Title Page

Statistical Analysis Plan

Study M14-748

An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Ombitasvir (OBV), Paritaprevir (PTV), Ritonavir (RTV) With or Without Dasabuvir (DSV) and With or Without Ribavirin (RBV) in Pediatric Subjects With Genotype 1 or 4 Chronic Hepatitis C Virus (HCV) Infection (ZIRCON)

Date: 31 May 2018

Version 1.0

2.0 Table of Contents

List of Tables

List of Figures

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by AbbVie Statistics and Statistical Programming for Study Protocol M14-748.
Study M14-748 is designed to evaluate the pharmacokinetics, safety, and efficacy of ombitasvir (OBV), paritaprevir (PTV), ritonavir (RTV) with or without dasabuvir (DSV) and with or without ribavirin (RBV) in pediatric subjects with genotype 1 or 4 chronic hepatitis C virus (HCV) infection.

The SAP provides details to guide the analyses for baseline, efficacy, and safety variables and describes the populations and variables that will be analyzed and the statistical methods that will be utilized. An interim analysis (after all subjects reach Post-Treatment [PT] Week 12 or prematurely discontinue the study) and an end of study analysis will be conducted for Study M14-748. 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 assess the pharmacokinetics of different OBV, PTV, RTV and DSV formulations with or without RBV in treatment-naïve, non-cirrhotic, GT 1 HCV-infected pediatric subjects in Part 1 and to assess the efficacy (percentage of subjects with SVR_{12} of all subjects) and safety of OBV/PTV/RTV with or without DSV and with or without RBV for 12 or 24 weeks in HCV GT1 or GT4-infected treatment-naïve and treatment-experienced pediatric subjects with and without compensated cirrhosis in Part 1 and Part 2.

The secondary objectives of this study are to evaluate the percentage of subjects with SVR_{12} by formulation, age and weight group and across all subjects on the adult formulation and to evaluate the percentage of subjects with SVR_{24} and the percentage of subjects with ALT normalization by the end of treatment, by formulation, age and weight group, and across all subjects on the adult formulation.

4.2 Design Diagram

The study aims to assess three formulations in the pediatric population. The approved adult 3D regimen formulation and the approved adult 2D regimen formulation will be administrated in subjects who are in the ≥ 12 to 17 age year group, weigh 45 kg or greater, and willing to swallow the adult formulation. The mini-tablet formulation will be administered in subjects who are in ≥ 3 to 8 and ≥ 9 to 11 age year groups in order to identify the optimal doses or final dose.

The study consists of three parts. In Part 1, a Phase 2 study, 36 or more eligible HCV GT1-infected, treatment-naïve, non-cirrhotic pediatric subjects will receive 12 weeks treatment with OBV/PTV/RTV with DSV and with or without RBV depending on HCV sub-genotype. At least 12 subjects in the ≥ 12 to 17 age year group who are ≥ 45 kg and willing to swallow the 3D adult formulation will be enrolled first to receive the 3D adult formulation. At least 12 subjects per each of the ≥ 9 to 11 and ≥ 3 to 8 age year groups will be enrolled to receive the mini-tablet formulation. Up to 12 additional pediatric subjects may be enrolled to receive mini-tablet in Part 1 if needed to adequately characterize the pharmacokinetics and determine the final dose strength for a particular age group or subgroup.

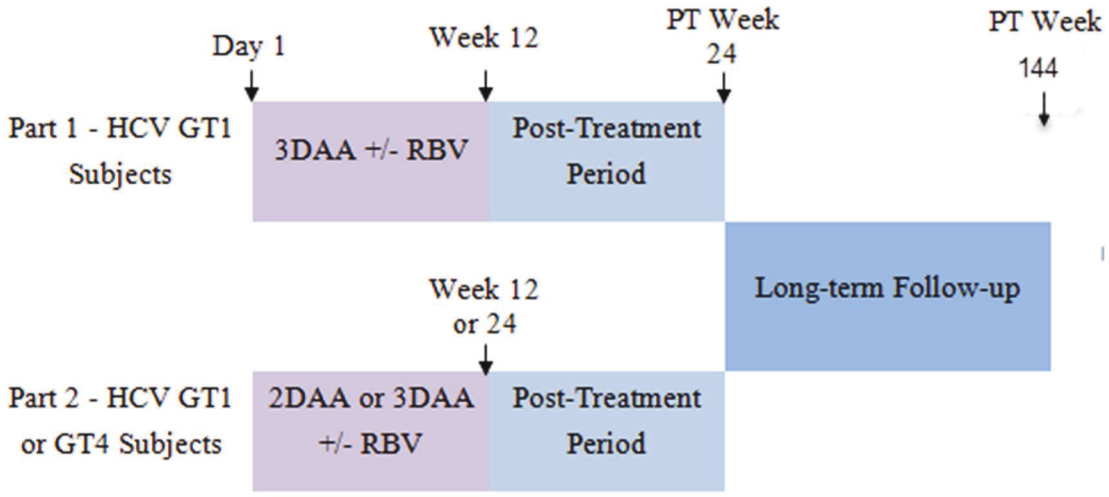
In Part 2, a Phase 3 study, eligible genotype 1 or 4-infected subjects will receive OBV/PTV/RTV with or without DSV and with or without RBV for 12 or 24 weeks treatment depending on HCV genotype, sub-genotype and cirrhosis status. Part 2 will evaluate the adult formulation in treatment-naïve and IFN treatment-experienced HCV GT1 or GT4-infected adolescents with or without compensated cirrhosis. Approximately 16 GT1 and 10 GT4 infected adolescents will be enrolled in Part 2.

In both Parts 1 and 2, if RBV is included in the treatment regimen, RBV will be provided as tablets to subjects who receive the adult formulation, and as 40 mg/ml oral solution to subjects who receive the mini-tablet.

Both Parts 1 and 2 will consist of a Screening Period, a Treatment Period, and a 24-week Post-Treatment Period. Subjects who take at least one dose of the study drug will be followed in the Post-Treatment Period. Subjects who prematurely discontinue study treatment in Part 1 will be followed in the Post-Treatment Period in Part 1. Similarly subjects who prematurely discontinue study treatment in Part 2 will be followed in the Post-Treatment Period in Part 2. After completing the Post-Treatment Period in Part 1 or Part 2, subjects will be followed in Part 3 the long-term follow-up period for another 120 weeks. Subjects who prematurely discontinue from the Post-Treatment Period in Part 1 or Part 2 or from Part 3 will be discontinued from the study.

After meeting the eligibility criteria, a total of approximately 62 subjects will be enrolled to 12 weeks of treatment in Part 1 or either 12 or 24 weeks of treatment in Part 2.

Figure 1. Study Schematic



The treatment duration will be 12 weeks for all subjects except HCV GT1a-infected subjects with cirrhosis; these subjects will receive treatment for 24 weeks.

The duration of the study will be 156 weeks (for subjects receiving a 12-week treatment) or 168 weeks (for subjects receiving a 24-week treatment), not including a screening

period of up to 42 days, consisting of a 12-week or 24-week Treatment Period and a Post-Treatment (PT) Period of 144 weeks in total for all subjects who receive at least one dose of study drug.

Subjects who meet the eligibility criteria will be enrolled in Part 1 or Part 2 to either 12 or 24 weeks of combination therapy with or without RBV based on HCV genotype, subtype, and cirrhosis status as described in Table 1.

Treatment Period

Table 1. Treatment Regimen and Duration by HCV Genotype, Subtype, and Cirrhosis Status

Patient Population	Treatment	Duration
Genotype 1b with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir (approved adult 3D formulation)	12 weeks
Genotype 1a,* without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin (approved adult 3D formulation plus RBV)	12 weeks
Genotype 1a,* with compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin (approved adult 3D formulation plus RBV)	24 weeks
Genotype 4 with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + ribavirin (approved adult 2D formulation plus RBV)	12 weeks

* Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 sub-genotype or with mixed genotype 1 infection.

All GT1- and GT4-infected adolescent subjects in Part 1 and Part 2 will receive OBV/PTV/r 25/150/100 mg once daily (QD) and GT1-infected adolescent subjects in Part 2 will receive also DSV 250 mg twice daily (BID). All adolescent subjects with HCV GT1a or GT4 infection will also receive RBV 1000 mg BID if weight is less than or equal to 75 kg or 1200 mg BID if weight is above 75 kg.

For subjects receiving mini-tablet formulation in Part 1, the doses will be dependent on the weight group (15 to 24 kg, 25 to 29 kg, 30 to 44 kg, ≥ 45 kg) at enrollment.

The Treatment Period will include assessment of PK, antiviral response, growth and development outcomes (assessed by height and Tanner pubertal stage), patient reported

outcomes (assessed by EuroQol 5 Dimensions 3 Levels Health State Instrument [EQ-5D-3L] questionnaire), HCC (assessed by liver ultrasound only in subjects with cirrhosis), acceptability questionnaires (for subjects receiving the min-tablet formulation only), and progression of liver disease (assessed by Fibrotest).

Post-Treatment Period

All subjects who receive at least one dose of study drugs will be monitored for an additional 24 weeks following the last dose of study drugs in Part 1 or Part 2. All subjects who complete the PT Week 24 visit in Part 1 or Part 2 will be followed till PT Week 144 in Part 3.

The Post-Treatment (PT) Period will include assessment of antiviral response, growth and development outcomes (assessed by height and tanner pubertal stage), patient reported outcomes (assessed by EuroQol 5 Dimensions 3 Levels Health State Instrument [EQ-5D-3L] questionnaire), HCC (assessed by liver ultrasound only for subjects with cirrhosis), and progression of liver disease (assessed by Fibrotest).

The PT Period will begin the day following the last dose of study drug treatment.

4.3 Sample Size

The sample size of 36 subjects in Part 1 will adequately characterize the pharmacokinetics of the AbbVie DAAs to enable dose selection in pediatric subjects.

According to the Prescribing Information of PEGASYS, the SVR_{24} rate in the NV17424 trial was 47% among 45 treatment-naïve pediatric subjects with HCV GT1. To show that the DAA regimen is superior to this standard of care by 20% in Parts 1 and 2, the lower bound of the 2-sided 95% confidence interval of the SVR_{12} rate across all subjects in the study must be greater than 67%. For the primary efficacy endpoint of the percentage of subjects with SVR_{12}, if it is assumed that 90% of subjects would achieve SVR_{12} then 50 or more subjects would have > 90% power to have a lower bound of 2-sided confidence interval based on normal approximation to the binomial distribution > 67%.

4.4 Planned Analysis

An interim analysis will occur after all subjects in Part 1 or Part 2 have completed the PT Week 12 Visit or prematurely discontinued from study. The database will be versioned after performing appropriate data cleaning. Final data through PT Week 144 will be locked in a later version of the database. SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. All statistical tests and all confidence intervals will be two-sided with an α level of 0.05.

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

There is no intention of changing the study design based on efficacy findings from the PT Week 12 interim analysis. The intention is to follow all subjects who receive study drug for at least 144 weeks following treatment. There will be no statistical adjustment employed due to this interim analysis.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

5.1.1 Intention-to-Treat (ITT) Population

The intention-to-treat (ITT) population will consist of all subjects who receive at least one dose of study drug in Part 1 or Part 2 of the study. All data from Part 1, Part 2, and Part 3 will be combined together, as appropriate, for statistical analyses specified in the SAP.

Demographic, baseline characteristic, exposure, concomitant medication and medical history analyses will be performed in the ITT population by age and weight group and overall among subjects on the mini-tablet formulation (ITT mini-tablet table with 6 columns), and in summary tables, by Part 1 vs Part 2 and overall for subjects on the adult formulation and overall among subjects on the mini-tablet formulation, and overall among all subjects (ITT summary table with 5 columns). Efficacy endpoints, growth and

development outcomes, and patient reported outcomes will be summarized in the ITT population. Acceptability questionnaire will be summarized overall and by age group among subject on the mini-tablet formulation in the ITT population.

In addition, sensitivity analyses of the percentage of subjects with SVR_{12}, will be performed on the Modified Intent-to-Treat Genotype (mITT-GT) population, and Modified Intent-to-Treat Genotype and Virologic Failure (mITT-GT-VF) population, respectively, as defined below.

The mITT-GT population includes subjects who receive at least 1 dose of study drug in Part 1 or Part 2 but excludes the subjects in Part 1 who are not of HCV GT1 infection and subjects in Part 2 who are not of HCV GT1 or GT4 infection. The mITT-GT population is used to reduce the risk of bias that could occur due to enrolled population deviating from the treatment regimen as specified by the protocol.

The mITT-GT-VF population includes all subjects who receive at least 1 dose of study drug but excludes the subjects in Part 1 who are not of HCV GT1 infection and the subjects in Part 2 who are not of HCV GT1 or GT4 infection and in either part excludes subjects who did not achieve SVR_{12} for reasons other than on treatment virologic failure or relapse. The mITT-GT-VF population is used to reduce the risk of bias that could occur due to either discordant HCV genotype or failures unrelated to study drug.

5.1.2 Safety Population

All subjects who receive at least one dose of study drug in Part 1 or Part 2 will be included in the safety population, which will be the same as the ITT population for this study.

Safety analyses will be performed on the safety population by age group and overall among subjects on the mini-tablet formulation, by Part 1 vs Part 2 and overall among subjects on the adult formulation, and overall among all subjects (Safety Summary 7 column table).

5.2 Variables Used for Stratification of Randomization

Approximately 62 subjects will be enrolled to receive ombitasvir, paritaprevir, ritonavir with or without dasabuvir and with or without RBV for 12 or 24 weeks depending on their HCV genotype, subtype, and cirrhotic status as shown in Table 1. No other stratification of enrollment will be used for this study, although dose will depends on age group and weight group that a subject falls in.

6.0 Analysis Conventions

6.1 Baseline and Final Value

6.1.1 Baseline

The baseline value refers to the last non-missing measurement collected before the first dose of study drug received in Part 1 or Part 2. All assessments on Study Day 1 should be performed prior to administering the first dose of study drug, in accordance with the protocol. The baseline value is therefore determined by the last non-missing measurement collected on or before the first day of study drug administration.

If multiple measurements are recorded on the same day, the last measurement recorded prior to dosing will be used as the baseline value. If these multiple measurements occur at the same time or time is not available, then the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be considered as the baseline value. This same baseline value will be used for Treatment and PT Periods.

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

6.1.2 Study Days

Study Days (days relative to the first dose of study drug) 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.

6.1.3 Study Drug End Days

For all subjects who receive at least one dose of study drug, study drug end days (days relative to the last dose of study drug) are calculated relative to the last dose of study drug. The last day of study drug 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.

6.1.4 Final Treatment Value

The final treatment value for each subject is the last measurement collected after Study Day 1 and on or before Study Drug End Day 2.

6.1.5 Final Post-Treatment Value

The final post-treatment value for each subject is the last measurement collected after Study Drug End Day 2.

6.2 Analysis Windows

For efficacy analyses of HCV RNA and resistance, the time windows specified in Table 2 and Table 3 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 blood sample collection date.

For safety laboratory data, vital signs (except height and waist circumference and the calculation of growth rate), and health-related quality of life (QoL) PROs collected throughout the study, the time windows specified in Table 4 will be used.

For height, waist circumference, the calculation of growth rate, and Tanner pubertal stage collected throughout the study, the time windows specified in Table 5 will be used. The growth rate will be calculated at each visit as the change in height (millimeter) over change in age (years) from the previous visit.

For acceptability questionnaire, the time windows specified in Table 6 describes how data are assigned to protocol specified time points during the treatment period.

For Fibrotest collected throughout the study, the time windows specified in Table 7 will be used.

If more than one assessment is included in a time window, the assessment closest 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. The only exception to this is for the SVR windows (e.g., SVR_4, SVR_{12}, and SVR_{24}); for these windows, 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 in analyses. For summaries of shifts from baseline and potentially significant values, multiple values on the same day will not be averaged; all values will be considered for these analyses.

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

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Day 1/Baseline[a]	1[a]	≤ 1[a]
Week 2	14	2 to 21
Week 4	28	22 to 42
Week 8	56	43 to 70
Week 12	84	71 to 98
Week 16[b]	112	99 to 126
Week 20[b]	140	127 to 154
Week 24[b]	168	155 to 182
Final Treatment Visit[c]		2 to ≤ 2 days after last dose of study drug

a. Day of first dose of study drug.

b. Applicable to subjects with 24 weeks of treatment.

c. The last value within the window will be used to define the Final Treatment visit value.

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 3. 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 1,176
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 for subjects who received at least one dose of study drug.

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

Note: The result closest to the scheduled time point will be used, except for SVR_4, 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 4. Analysis Time Windows for Laboratory Data, Vital Sign (Except Height, Waist circumference, and the Calculation of Growth rate), and PRO Instruments

Scheduled Visit[a]	Nominal Day (Study Day)	Time Window (Study Days Range)
Day 1/Baseline	1[b]	≤ 1[b]
Week 2	14	2 to 21
Week 4	28	22 to 42
Week 8	56	43 to 70
Week 12	84	71 to 98
Week 16[c]	112	99 to 126
Week 20[c]	140	127 to 154
Week 24[c]	168	155 to 182
Final Treatment Visit[d]		2 to ≤ 2 days after last dose of study drug
Scheduled Visit	**Nominal Day (Study Drug End Day)**	**Time Window (Study Drug End Days Range)**
Post-Treatment Week 4	28	3 to 56
Post-Treatment Week 12	84	57 to 126
Post-Treatment Week 24	168	127 to 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 1,176
Final Post-Treatment Visit[e]		> 2 days after last dose of study drug

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

b. Day of first dose of study drug.

c. Applicable to subjects with 24 weeks of treatment.

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.

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

Note: The result closest to the scheduled time point will be used. For visits through Treatment Week 24, data must also be within 2 days after the last dose of study drug. For post-treatment visits, data must also have Study Drug End Day > 2 where Study Drug End Day 0 is defined as the day of the last dose of study drug.

Lab data are collected only through Post-Treatment Week 4.

Acceptability questionnaire is collected on Treatment Weeks 2, 12, and 24 if applicable for subjects taking the min-tablet formulation only.

Table 5. Analysis Time Windows for Height, Waist Circumference, the Calculation of Growth Rate, and Tanner Pubertal Stage

Scheduled Visit[a]	Nominal Day (Study Day)	Time Window (Study Days Range)
Day 1/Baseline	1[b]	≤ 1[b]
Scheduled Visit	**Nominal Day (Study Drug End Day)**	**Time Window (Study Drug End Days Range)**
Post-Treatment Week 12	84	3 to 168
Post-Treatment Week 36	252	169 to 462
Post-Treatment Week 96	672	463 to 840
Post-Treatment Week 144	1,008	841 to 1,176
Final Post-Treatment Visit[c]		> 2 days after last dose of study drug

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

b. Day of first dose of study drug.

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

Note: The result closest to the scheduled time point will be used. For post-treatment visits, data must also have Study Drug End Day > 2 where Study Drug End Day 0 is defined as the day of the last dose of study drug.

Tanner pubertal stage is collected for all subjects with age ≥ 9 to 17 year old. If a subject turns 9 year old during the study, the test will start to be performed after the subject turns 9 year old. Once a child reaches Tanner Stage 5, the test will not be repeated.

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 6. Analysis Time Windows for Acceptability Questionnaire (Treatment Period Only)

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Week 2	14	2 to 35
Week 12	84	57 to 126
Week 24[a]	84	127 to 182
Final Treatment Visit[b]	2 to ≤ 2 days after last dose of study drug	

a. For 24-week treatment only.

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

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used. Palatability questionnaire are administrated to subjects in Part 2 at Week 2 and End of Treatment Visit or premature discontinuation visit.

Table 7. Analysis Time Windows for Fibrotest

Scheduled Visit[a]	Nominal Day (Study Day)	Time Window (Study Days Range)
Day 1/Baseline	1[b]	≤ 1[b]
Scheduled Visit	**Nominal Day (Study Drug End Day)**	**Time Window (Study Drug End Days Range)**
Post-Treatment Week 24	168	3 to 420
Post-Treatment Week 96	672	421 to 840
Post-Treatment Week 144	1,008	841 to 1,176
Final Post-Treatment Visit[c]		> 2 days after last dose of study drug

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

b. Day of first dose of study drug.

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

Note: The result closest to the scheduled time point will be used. For post-treatment visits, data must also have Study Drug End Day > 2 where Study Drug End Day 0 is defined as the day of the last dose of study drug.

6.3 Missing Data Imputation

No data will be imputed for any efficacy or safety analyses except for analyses of the HCV RNA endpoints.

Missing Data Imputation for SVR

HCV RNA values will be selected for analysis based on the analysis windows defined in Section 6.3.

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.

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

The ITT population and 2 ITT population table formats will be used to summarize demographics, baseline characteristics, medical history and previous, concomitant, and post-treatment medications; i.e., data will be summarized by age and weight group and overall among all subjects on the mini-tablet formulation; and by Part 1 vs Part 2 and

overall among subjects on the adult formulation, and overall among subjects on mini-tablet formulation and overall among all subjects.

7.1 Demographic and Baseline Characteristics

Demographics include age, birth year, weight, height, BMI, height z score (height z score will be calculated using WHO published height-for-age z-score tables),[6] and waist circumference as continuous variables, and sex, race, ethnicity, geographic region and country, age category ([≥ 3 - 8 year old group], [≥ 9 - 11 year old group], and [≥ 12 - 17 year old group]), weight category 15 to 29 kg, 30 to 44 kg, ≥ 45 kg), and height z-score category (< –1, –1 to 1, > 1).

Baseline characteristics will include: HCV genotype subtype (1a, 1b, 1-other, and 4; using central laboratory results and final genotype/subtype results, see Section 10.10), IL28B genotype ([CC, CT, or TT] and [CC or non CC]),]), prior IFN treatment history (treatment-naïve or IFN-based treatment-experienced), response to prior IFN treatment (prior non responder {null responder, partial responder, or other unable to specify}, breakthrough, relapse, unknown and interferon experienced-other), baseline platelet count (continuous and [< 90 × 10^9/L, ≥ 90 × 10^9/L], baseline albumin (continuous and [< 35, ≥ 35 g/L]), baseline creatinine clearance using the Schwartz method for subjects from 3 to < 12 years old (continuous and [< 30, ≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73 m^2]) and using the CC&G method for subjects at least 12 years old (continuous; and [< 30 mL/min, ≥ 30 – < 50 mL/min, ≥ 50 – 8 < 90 mL/min, ≥ 90 mL/min]) baseline HCV RNA levels ([continuous (use $\log_{10}$ HCV RNA)] and [< 800,000 IU/mL or ≥ 800,000 IU/mL]), baseline fibrosis stage (F0 - 1, F2, F3, F4), baseline Fibrotest score (continuous and [< 0.49, 0.49 – 0.58, 0.59 – 0.74, ≥ 0.75]), baseline Child-Pugh score (non-cirrhotic, 5, 6, or > 6), tobacco use (current, former, never or unknown) status, alcohol use (current, former, never or unknown) status, and baseline Tanner pubertal staging – genital (males only) (stages 1 - 5), breast (females only) (stages 1 - 5), and pubic hair development (stages 1 - 5).

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, NS5A, and/or NS5B sequences performed by AbbVie. If the phylogenetic analysis is available it will be used to determine the subject's final HCV genotype and subtype. If it is not available, then the Sanger 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 assay results are available, then the Inno-LIPA assay results will be used to categorize the subject.

Subjects' baseline fibrosis stage will be assessed by investigator during the screening period and categorized as F0 - 1, F2, F3, or F4.

Summary statistics (N, mean, median, standard deviation [SD], and range) will be generated for continuous variables (e.g., age and BMI) and the number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

7.2 Medical History

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

7.3 Previous Treatment and Concomitant Medications

Prior and concomitant medications will be summarized. 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 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 (maximum) dose of study drug. The number and percentage of subjects taking prior or concomitant medications will be summarized by generic drug name based on the WHO Drug Dictionary. Note that prior HCV medications (IFN and RBV) will be summarized separately from other prior medications.

Medications for the treatment of HCV taken in the PT Period will be collected and will be summarized by generic drug name. 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.

8.0 Patient Disposition

All patient disposition summaries will be performed in the safety population using the safety population table format. The number of subjects for each of the following categories will be summarized.

- Enrolled Subjects;
- Subjects who took at least one dose of study drug;
- Subjects who completed study drug;
- Subjects who discontinued from 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 the interim analysis);

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

The number and percentage of subjects will be summarized for:

- Subjects with interruptions of all study drugs for toxicity management;

- Subjects with any RBV dose modification;
  - Subjects with RBV dose modification due to decrease in hemoglobin;
  - Subjects with RBV dose modification due to decrease in creatinine clearance;
  - Subjects with RBV dose modification due to weight change;
  - Subjects with RBV dose modification due to other reasons;
- Subjects with any RBV dose modification to 0 mg (i.e., RBV interruptions).

Reasons for study drug interruption and RBV dose modifications will be presented in the CSR listings.

The number and percentage of screened subjects who screen failed will be calculated, and the reasons for screen failure (inclusion/exclusion criteria, withdrew consent, lost to follow-up, and/or other) will be summarized. A listing of reasons for screen failure will be provided for all subjects who screen failed.

9.0 Study Drug Exposure and Compliance

Exposure and compliance will be summarized in the safety population using the safety population format.

9.1 Exposure

Duration of exposure is defined for each subject as the last study drug dose date minus the first study drug dose date plus 1 day.

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be presented. Study drug duration also will be summarized with frequencies and percentages using the following categories depending on the treatment duration:

- 12 weeks of treatment: 1 to 15 days, 16 to 30 days, 31 to 45 days, 46 to 60 days, 61 to 76 days, and > 76 days.
- 24 weeks of treatment: 1 to 15 days, 16 to 30 days, 31 to 60 days, 61 to 90 days, 91 to 120 days, 121 to 153 days, and > 153 days.

9.2 Compliance

For ombitasvir/paritaprevir/r tablet, dasabuvir tablet, and RBV tablet, tablet is the dose unit for drug accountability. For mini-tablets, bottle 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. A mini-tablet bottle is considered to be taken only if the return status is empty. For RBV solution, mL is the dose unit for drug accountability.

At each protocol-specified visit, the total number of dose units dispensed and returned is recorded for each type of study drug. The compliance for each type of dose unit within the Treatment Period will be calculated as the percentage of dose units taken or returned empty relative to the total number of 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 – date of first dose + 1 day). If a mini-tablet bottle is returned unsealed but not empty or if any dosing unit of study drug is not returned for reconciliation, then study drug compliance for that drug will not be calculated for that subject. Study drug interruptions due to an adverse event or other planned interruptions for toxicity management recorded on the eCRF will be subtracted from the duration. For compliance to RBV, RBV dose modifications due to adverse events, toxicity management, or weight changes as recorded on the RBV Dose Modifications eCRF will be used to modify the total number of unit that should have been taken. 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 will be summarized with the N, mean, standard deviation, median, minimum, and maximum. In addition, the percentage of compliant subjects will be calculated for each study drug.

10.0 Efficacy Analysis

10.1 General Considerations

All efficacy analyses will be performed in 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 HCV RNA 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.

A confirmed quantifiable value during treatment is defined as any two consecutive HCV RNA measurements ≥ LLOQ (or 100 IU/mL for **Breakthrough**), either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement. A confirmed quantifiable post-treatment value is defined as any two consecutive post-treatment HCV RNA measurements ≥ LLOQ.

Breakthrough = confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during the Treatment Period; or confirmed increase from nadir in HCV RNA (two consecutive

HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during the Treatment Period. A single breakthrough value (≥ 100 IU/mL or > 1 $\log_{10}$ above nadir) followed by lost to follow-up also will be considered a breakthrough (i.e., will not require confirmation).

EOT failure = HCV RNA ≥ LLOQ at end of treatment with at least 6 weeks of treatment, where the HCV RNA value must be collected on or after Study Drug Day 36 and study drug duration ≥ 36 days.

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

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

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

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

$Relapse_{12}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR_{12} window) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment excluding reinfection as described below.

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

Relapse$_{overall}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the 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 77 days or greater for subjects assigned to 12 weeks of treatment, and 154 days or greater for subjects assigned to 24 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 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 < 77 days for subjects assigned to 12 weeks of treatment or duration < 154 days for subjects assigned to 24 weeks of treatment] and did not meet the **On-treatment virologic failure or HCV reinfection definitions**);
5. Missing follow-up data in the SVR_{12} window (defined as any subject who completed study drug without data in the SVR_{12} window after applying the imputation rules and not meeting the definitions of [1], [2], [3], or [4]);
6. Other (defined as 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 re-infection;
3. $Relapse_{12}$;
4. $Relapse_{24}$;
5. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{24} non-responder who prematurely discontinued study drug

[study drug duration < 77 days for subjects assigned to 12 weeks of treatment or duration < 154 days for subjects assigned to 24 weeks of treatment] and did not meet the **On-treatment virologic failure**, **HCV reinfection, Relapse$_{12}$**, or **Relapse$_{24}$** definitions);

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

This study will proceed using a sequential testing procedure from testing the hypothesis for the primary efficacy endpoint that the SVR_{12} rate is 20% > than the pre-specified historical control rate of 47% to the hypothesis for the secondary efficacy endpoint that the SVR_{24} rate is 20% > than the pre-specified historical control rate of 47%. Thus, the testing of the secondary hypothesis regarding SVR_{24} will only be performed in the lower confidence bound of the 2-sided 95% confidence interval of the SVR_{12} rate is > 67%.

10.3 Primary PK and Primary Efficacy Analysis

10.3.1 Primary PK Analysis

The primary PK endpoints from Part 1 are:

- C_{max} and AUC following dosing on Week 2, and trough concentration following dosing on Week 2 and Week 8 for OBV, PTV, DSV, and RTV.

For the intensive PK data at Week 2, the pharmacokinetic parameters of C_{max}, T_{max} and AUC will be calculated and summarized for each analyte (paritaprevir, ombitasvir, ritonavir, dasabuvir, and dasabuvir M1 metabolite, and RBV, as applicable based on DAA regimen).

The trough concentrations at Week 8 will be summarized for each analyte.

10.3.2 Primary Efficacy Analysis Across Parts 1 and 2.

The primary efficacy endpoint across Parts 1 and 2 is:

- The percentage of subjects with SVR_{12} among all subjects.

The SVR_{12} rate and corresponding 2-sided 95% confidence interval will be presented.

For both the primary and secondary efficacy endpoints, the Wilson's score method will be used to calculate the confidence interval.

According to the Highlights of Prescribing Information of PEGASYS®, the SVR_{24} rate was 47% among 45 treatment-naïve pediatric subjects with HCV GT1 in the NV17424 trial.[6] To show that the DAA regimen is superior to this current standard of care by 20%, the lower bound of the 2-sided 95% confidence interval of the SVR_{12} rate across all subjects in the study must be greater than 67%.

10.4 Secondary Efficacy Analyses Across Parts 1 and 2

The secondary efficacy endpoints calculated across subjects in Parts 1 and 2 are:

1. The percentage of subjects who achieve SVR_{12} by formulation, age and weight group, and across all subjects on the adult formulation.
2. The percentage of subjects who achieve SVR_{24} by formulation, age and weight group, and across all subjects on the adult formulation.
3. The percentage of subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline,

by formulation, age and weight group, and across all subjects on the adult formulation.

For the percentage of subjects with SVR_{12} or SVR_{24} and the percentage of subjects with ALT normalization during treatment, the simple percentage will be calculated along with the 2-sided 95% confidence intervals.

To test the hypothesis that the percentage of HCV pediatric subjects treated with ombitasvir/paritaprevir/r, with or without dasabuvir with or without RBV who achieve SVR_{24} is superior to the historical SVR rate of 47% for the pediatric population treated with pegIFN and RBV by 20%, the lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate across all subjects in the study will also be compared to 67%.

ALT normalization is defined as the percentage of subjects with ALT at or below the ULN at the final treatment visit among subjects with ALT > ULN at baseline, and will be presented along with 95% confidence intervals.

The concordance between SVR_{12} and SVR_{24} will be assessed by agreement between SVR_{12} and SVR_{24} and by the positive predictive value (PPV) and the negative predictive value (NPV) of SVR_{12} on SVR_{24}. The agreement between SVR_{12} and SVR_{24} is defined as the number of subjects achieving both SVR_{12} and SVR_{24} and the number of subjects not achieving both SVR_{12} and SVR_{24} out of all subjects in the ITT population. 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 do not achieve SVR_{12}.

10.5 Efficacy Subgroup Analysis

The number and percentage of subjects with SVR_{12} across all subjects in the ITT population will be presented by the following subgroups:

- Age group (≥ 3 – 8, ≥ 9 – 11, and ≥ 12 – 17 years) and weight group (15 to 29 kg, 30 to 44 kg, ≥ 45 kg) at enrollment;

- HCV genotype and sub-genotype (1a, 1b, other 1, and 4);
- Prior HCV Treatment Experience (naïve, IFN-experienced)
- Prior IFN treatment response (among experienced) (prior non-responder, prior breakthrough, prior relapse, unknown, and interferon experienced-other);
- IL28B genotype (CC or non-CC), (CC, CT, or TT);
- Sex (male or female);
- Baseline fibrosis stage (F0-F1, F2, F3 or F4);
- Baseline HCV RNA level (< 800,000 IU/mL or ≥ 800,000 IU/mL; < median or ≥ median);
- Race (Black versus non-black);
- Ethnicity (Hispanic/Latino versus none);
- Baseline height z-score (< –1, –1 to 1 or > 1);
- Drug compliance (< 80% versus ≥ 80%).
- Baseline creatinine clearance using the CC&G method for subjects at least 12 years old (< 50 mL/min, ≥ 50 mL/min);
- Baseline creatinine clearance using the Schwartz method for subjects from 3 to < 12 years old (< 60 mL/min/1.73 m^2, ≥ 60 mL/min/1.73 m^2)
- RBV dose modifications (yes/no).

The 2-sided 95% Wilson score confidence interval will be produced for each subgroup with at least 10 subjects.

In addition, stepwise logistic regression will be performed on virologic failure (on-treatment virologic failure or relapse) using subgroup variables as described above, if there are sufficient number of virologic failures. Some variables may be treated as continuous to decrease the chance of separation or quasi-separation and some variables may be eliminated if missing for too many subjects.

10.6 Sensitivity Analysis for the Efficacy Endpoint of SVR_{12}

In addition to presenting the primary efficacy endpoint of SVR_{12} as described in Section 10.4, two sensitivity analyses of SVR_{12} will be presented using the two modified populations – mITT-GT and mITT-GT-VF.

10.7 Additional Efficacy Analyses

The following efficacy endpoints will be analyzed by formulation, age and weight group, and across all subjects on the adult formulation:

1. The percentage of subjects with virologic failure during treatment;
2. The percentage of subjects with Post-Treatment relapse (including $Relapse_{12}$ as defined at the end of this section);
3. The percentage of subjects who relapsed after achieving SVR_{12} (**$Relapse_{24}$**).
4. The percentage of subjects with HCV RNA < LLOQ at each post baseline visit during the Treatment Period (using data as observed);
5. The change from baseline to all post-baseline visits in Fibrotest score.

All rates of SVR, ALT normalization, virologic failure on treatment and relapse will be presented with 2-sided 95% confidence intervals using the Wilson's method. Imputations for missing data will be performed as described in Section 6.3 for analysis of SVR and relapse. All other endpoints will be presented using data as observed.

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 < 77 days for subjects assigned to 12 weeks of treatment) will be provided, as applicable.

Summary statistics (n, mean, SD, median, minimum and maximum) at each applicable visit and for change from baseline to each applicable visit will be provided by fibrosis stage and SVR_{12} for Fibrotest score.

10.8 Treatment Failures

The number and percentage of subjects meeting each and any of the SVR_{24} and SVR_{12} non-response categories as defined in Section 10.1 will summarized by formulation, age and weight group, and across all subjects on the adult formulation along with the 2-sided 95% confidence interval using the Wilson's score method and a corresponding list of the subjects numbers.

10.9 Growth and Development

The following growth and development endpoints will be calculated at applicable study visits.

- Growth rate at each post baseline visit (defined as change in height over change in age from the previous visit)
- Height z score[6]
- Waist circumference
- Tanner staging

For growth rate, summary statistics (N, mean and SD together, median and range together) will be provided at each applicable post baseline visit for all and by gender for each pre-defined age group separately. For height z score, summary statistics (N, mean and SD together, median and range together) of height z score and summary statistics (N, mean and SD together, median and range together) of change from baseline will be provided over time at each applicable study visit for all and by gender each for pre-defined age group separately. Change from baseline in waist circumference, weight

and height will be summarized together with other vital signs such as temperature and blood pressure. Listings of Tanner staging for each applicable subject over applicable timepoints will be produced.

10.10 Resistance Analyses

If possible, subjects treated with study drug during the Treatment Period who experience virologic failure will have resistance testing conducted if 1) they have on-treatment breakthrough; 2) if they have post-treatment relapse, with a study drug duration ≥ 77 days for subjects assigned to 12 weeks of treatment or with a study drug duration ≥ 154 days for subjects assigned to 24 weeks of treatment; or 3) if they have at least 6 weeks of treatment and fail to suppress by Week 6 (i.e., meet virologic stopping criteria). Subjects meeting one of these criteria will be referred to as subjects in the primary virologic failure (PVF) population, and a listing by subject that includes HCV subtype, IL28B genotype, reason for 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 subtype and reason for non-response in the subject identifier for each subject. A separate listing will delineate all subjects in the PVF population for whom no sequencing was performed (e.g., lost to follow-up while HCV RNA ≤ 1000 IU/mL).

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

The regions of interest for population sequencing from all evaluated time points in this study are those encoding full length NS3/4A, NS5A, and NS5B. The prototypic reference sequences used for analysis will be H77 for genotype 1a or Con1 for genotype 1b.

For each DAA target, resistance-associated signature amino acid variants will be identified by AbbVie Clinical Virology. Amino acid positions where resistance

associated variants have been identified in vitro and/or in vivo are 1) for ABT-450: 36, 43, 55, 56, 80, 155, 156, and 168 in NS3 for genotype 1a; 55, 56, 155, 156, and 168 in NS3 for genotype 1b; 56, 155, 156, and 168 for genotype 4; 2) for ABT-267: 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93 in NS5A for genotype 1a; 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93 in NS5A for genotype 1b; 28, 30, 31, 58, and 93 for genotype 4; and 3) for ABT-333: 316, 414, 446, 448, 451, 553, 554, 555, 556, 558, 559, and 561 in NS5B for genotype 1a; 316, 368, 411, 414, 445, 448, 553, 556, and 559 in NS5B for genotype 1b. The final list of amino acid positions where resistance-associated variants have been identified will be included in the CSR.

The following definitions will be used in the resistance analyses:

- Baseline variant: a variant (by population sequencing) in a baseline sample determined by comparison of the amino acid sequence of the baseline sample to the appropriate prototypic reference amino acid sequence for a given DAA target (NS3, NS5A, or NS5B).
- Post-baseline variant by population sequencing: an amino acid variant in a post baseline time point sample that was not detected at baseline in the subject and is detectable by population sequencing.
- Emerged variant by population sequencing: a post-baseline variant that is observed in 2 or more subjects of the same subtype by population sequencing.
- Linked variant by population sequencing: 2 or more signature resistance associated or emerged amino acid variants identified within a target by population sequencing, and no mixture of amino acids is detected at either position.

The following analyses will be performed on the samples from subjects who are in the PVF population and have baseline and post-baseline resistance data available.

The HCV amino acid sequence as determined by population sequencing at baseline will be compared to the appropriate prototypic reference amino acid sequence. A listing by subject of all baseline variants relative to prototypic reference sequence at signature

resistance-associated amino acid positions will be provided for each DAA target (NS3, NS5A, and NS5B – genotype 1 only).

The HCV amino acid sequence as determined by population sequencing at the time of VF or the sample closest in time after VF with an HCV RNA level of ≥ 1000 IU/mL will be compared to the baseline and appropriate prototypic reference amino acid sequences. A listing by subject and time point of all post-baseline variants relative to the baseline amino acid sequences will be provided across all DAA targets (NS3, NS5A, and NS5B). In addition, a listing by subject and time point of all post-baseline variants at signature resistance amino acid positions relative to the appropriate reference sequence will be provided across all DAA targets (NS3, NS5A, and NS5B – genotype 1 only).

The number and percentage of subjects with post-baseline variants at signature amino acid positions or emerged variants at non-signature amino acid positions by population sequencing, listed by amino acid position and variant within a DAA target at the time of VF compared to baseline will be summarized, along with the number of subjects within a DAA target and overall. The analyses will be grouped by HCV subtype and DAA target (NS3, NS5A, or NS5B – genotype 1 only) and will list the numbers of subjects with each variant. The number of subjects with resistance variants in 3 targets – (genotype 1 only), 2 targets or 1 target will also be provided.

Linkage between emerged or signature variants by population sequencing will also be evaluated. A listing by subject and time point of the linked variants by population sequencing for each target will be provided.

For all subjects who experience VF, the persistence of resistance-associated variants for each target (NS3, NS5A, and NS5B – genotype 1 only) will be assessed by population sequencing at Post-Treatment Week 24. Listings by subject of all treatment emergent variants at signature resistance-associated positions will be provided for each DAA target.

10.11 Patient Reported Outcomes

During Treatment and Post-Treatment, health utility values will be assessed using the EQ-5D-3L instrument. The health state data measured by EQ-5D-3L will be analyzed using adult weights until validated weights are available for pediatric subjects to convert health states to a single summary index.

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 country-specific weights (if available) or US weights (if not available). The VAS score will be analyzed separately.

For subjects enrolled in Part 1 and 2 (ITT), summary statistics at each visit and on the change from baseline to each visit (n, mean, SD, median, minimum and maximum) of EQ VAS score will be provided overall and by age group. In particular, for each of the three visits – EOT, PT Week 12 and PT Week 24, the mean change from baseline in EQ VAS score, will be compared between subjects who achieve SVR_{12} and those who do not using ANCOVA with SVR_{12} status as a factor, and appropriate baseline fibrosis stage, gender, age group, and EQ VAS score as covariates. Point estimate of the mean difference and 95% confidence intervals will be provided using the subjects who do not achieve SVR_{12} as the reference group. For subjects enrolled in Part 3 (ITT-3), summary statistics at each visit after PT Week 24 and the change from baseline to each applicable visit after PT Week 24 (n, mean, SD, minimum and maximum) in EQ VAS score will be provided. The ANCOVA analyses will be performed only if there is a sufficient number of subjects who didn't achieve SVR_{12}.

10.12 Acceptability Questionnaires

The analyses of acceptability questionnaires will be performed among subjects who received the mini-tablet in the ITT population.

The number and percentage of subjects with each categorical answer marked will be presented for each question in the acceptability questionnaire at each applicable treatment visit overall, and by age and weight group. Listings of acceptability questionnaire results and comments for each applicable subject over applicable treatment visits will be produced separately for each formulation.

11.0 Safety Analysis

11.1 General Considerations

The safety analysis will be carried out for all subjects in the safety population using the safety population table format.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of study drug through 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).

11.2.1.1 Tabulations of Treatment-Emergent Adverse Events

Adverse event data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the clinical study report. 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 adverse events will be presented consisting of the number and percentage of subjects experiencing at least one event for the following adverse event categories:

- Any treatment-emergent adverse event;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to RBV;
- Treatment-emergent adverse events of grade 3 or higher;
- Treatment-emergent adverse events of Grade 3 or higher with a "reasonable possibility" of being related to DAAs
- Serious treatment-emergent adverse events;
- 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 RBV dose modifications;
- Treatment-emergent adverse events leading to death;
- Deaths.

Adverse Event by SOC and PT

The following summaries of adverse events will be generated:

- Treatment-emergent adverse events;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to RBV;
- Serious treatment-emergent adverse events;
- 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;
- 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 RBV dose modifications;
- Treatment-emergent adverse events leading to death;
- Treatment-emergent adverse events leading to concomitant medication use (events with other action taken of "concomitant medication prescribed").

For all adverse event summaries, the number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to SOC and PT. Subjects reporting more than one adverse event for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one adverse event will be counted only once in the overall total.

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

Adverse Event by PT

The number and percentage of subject experiencing treatment-emergent adverse events will be tabulated according to preferred term and sorted by overall frequency. Similar summaries will be provided for Grade 3 or higher treatment-emergent adverse events, DAA related treatment-emergent adverse events, and treatment-emergent adverse events of Grade 3 or higher with a "reasonable possibility" of being related to DAA.

Adverse Event of Special Interest

Specific AEs of special interest will be identified by the following search criteria:

Adverse Event of Special Interest	Search Criteria	Time Frame
Hepatic decompensation and hepatic failure	PMQ "Hepatic decompensation and hepatic failure"	Treatment-emergent
Hepatocellular carcinoma	Cases will be identified by the following MedDRA preferred terms: hepatic cancer recurrent, hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, and hepatic cancer metastatic	All post-baseline cases including both treatment emergent and non-treatment emergent
Severe cutaneous reactions	SMQ "Severe cutaneous adverse reactions" (narrow search)	Treatment-emergent

For each AE of special interest, the number and percentage of subjects experiencing at least one adverse event of special interest will be presented by SOC and PT. A listing of adverse events for subjects meeting the search criterion will be provided for each adverse event of special interest.

Adverse Event by Maximum Severity Grade Level

Treatment-emergent adverse events and DAA-related treatment emergent adverse events will be summarized by maximum severity grade level. 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 DAA study drug and RBV, 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.

11.2.2 Listing of Adverse Event

Listings of all serious adverse events (from the time the subject signed the study-specific informed consent until 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 interruptions, treatment-emergent adverse events leading to RBV dose modifications and treatment-emergent adverse events of special interest will be provided.

11.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional lab testing due to all SAE will be used in all analysis.

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, absolute neutrophil count (ANC), reticulocyte count, prothrombin time, INR, and activated partial thromboplastin time (aPTT).

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, serum glutamic pyruvic transaminase (SGPT/ALT), serum glutamic oxaloacetic transaminase (SGOT/AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, uric acid, cholesterol, total protein, glucose, triglycerides, albumin, chloride, bicarbonate, magnesium, gamma glutamyl transferase (GGT), creatinine clearance (CC&G formula) for subjects at least 12 years old, and creatinine clearance adjusted for body surface area (BSA) using the Schwartz formula for subjects between 3 and < 12 years old.

For subjects at least 12 years old, the central lab calculates the estimated creatinine clearance (CrCl) based on the following CC&G formula:

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

For subjects between 3 and < 12 years old, the central lab calculates CrCl adjusted for BSA based on the following Schwartz formula:

> CrCl using Schwartz formula (mL/min/1.73 m^2) = 0.55 × (height in centimeter) / [serum creatinine (mg/dL)].

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

The criteria for potentially clinically significant (PCS) laboratory findings are described in Table 8 and Table 9.

Table 8. Criteria for Potentially Clinically Significant Hematology Values

Test/Units	Age[a] Range (Years) and Gender if applicable	Very Low (VL)	Very High (VH)
Hemoglobin			
(g/dL)	3 - 11	< 11.5	
(g/dL)	12 - 17 Female	< 12.0	
(g/dL)	12 - 17 Male	< 13.0	
Platelets Count			
(cells/mm^3)		< 50,000	
(cells/L)		$< 50 \times 10^9$	
White Blood Cell Count			
(cells/mm^3)		< 2000	> 20,000
(cells/L)		$< 2.0 \times 10^9$	$> 20 \times 10^9$
Absolute Neutrophil Count			
(cells/mm^3)		< 1000	
(cells/L)		$< 1 \times 10^9$	
Lymphocyte Count			
(cells/mm^3)		< 500	
(cells/L)		$< 0.5 \times 10^9$	
Eosinophil Count			
(cells/mm^3)			> 5000
(cells/L)			$> 5 \times 10^9$
aPTT			> 2 × ULN
International Normalized Ratio			> 2 × ULN

a. Use baseline age.

Note: A post-baseline value must be more extreme than the baseline value to be considered a PCS finding.

Table 9. Criteria for Potentially Clinically Significant Chemistry Values

Test/Units	Very Low (VL)	Very High (VH)
ALT/SGPT		> 5 × ULN and ≥ 2 × baseline
AST/SGOT		> 5 × ULN and ≥ 2 × baseline
Alkaline Phosphatase		> 1.5 × ULN
Total Bilirubin (mg/dL)		≥ 2.0 × ULN
Creatinine		
(mcmol/L)		≥ 132.605
(mg/dL)		≥ 1.5
Creatinine Clearance (mL/min)	< 50	
BUN		> 5 × ULN
Uric Acid		
(mcmol/L)		> 713.817
(mg/dL)		> 12.0
Phosphate		
(mmol/L)	< 0.6	
(mg/dL)	< 2.0	
Calcium, Serum		
(mmol/L)	< 1.75	> 3.1
(mg/dL)	< 7.0	> 12.5
Sodium (mmol/L)	< 130	> 155
Potassium (mmol/L)	< 3.0	> 6.0
Glucose		
(mmol/L)	< 2.2	> 13.9
(mg/dL)	< 40	> 250
Albumin		
(g/L)	< 20	
(g/dL)	< 2	
Protein		
(g/L)	< 50	
(g/dL)	< 5.0	

Table 9. Criteria for Potentially Clinically Significant Chemistry Values (Continued)

Test/Units	Very Low (VL)	Very High (VH)
Cholesterol		
(mmol/L)		> 10.34
(mg/dL)		> 400
Triglycerides		
(mmol/L)		> 5.7
(mg/dL)		> 500

Note: A post-baseline value must be more extreme than the baseline value to be considered a PCS finding.

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. 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 number and percentage of subjects with post-baseline values during the Treatment Periods meeting the specified criteria for Potentially Clinically Significant (PCS) laboratory values (defined in Table 8 and Table 9) will be summarized. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A separate listing will be provided that presents all lab values for the subjects meeting PCS criteria during treatment.

The laboratory parameters defined in Table 10 will be assigned a toxicity grade of 1, 2, 3, or 4 based on National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4. The number and percentage of subjects with a maximum toxicity

grade of 1, 2, 3 or 4 will be summarized. 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 10. 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 10.

Table 10. Definitions of CTCAE Grades 1, 2, 3, and 4

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT/SGPT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
AST/SGOT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Alkaline Phosphatase	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
Total Bilirubin	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN
Hemoglobin Decreased	< LLN – 100 g/L	< 100 – 80 g/L	< 80 – 65 g/L	< 65 g/L

Assessment of Hepatic Laboratory Values

The number and percentage of subjects with post-nadir (preceding value is lower than the subsequent) on-treatment increases in ALT and/or post baseline increases in total bilirubin meeting the following criteria for potential hepatotoxicity will be summarized:

- post nadir ALT > 5 × ULN (regardless of grade change);
- total bilirubin ≥ 2 × ULN and > baseline
- 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)

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 as meeting the specified criteria regardless of the baseline bilirubin value, except for the 2nd bullet above where the post-baseline bilirubin value must be worse than the baseline bilirubin value.

Listings of 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 assessment of hepatic laboratory value criteria defined above.

Hepatic Laboratory Abnormalities of Interest

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

- confirmed post-nadir ALT > 5 × ULN;
- post nadir ALT > 3 × ULN and a concurrent (determined by examination of listing) total bilirubin > 2 × ULN with direct bilirubin:total bilirubin ratio > 0.4

This listing of the assessment of hepatic laboratory values will include all the cases of hepatic laboratory of abnormalities of interest.

Confirmed post nadir ALT > 5 × ULN is defined as two consecutive ALT measurements > 5 × ULN after the nadir (which can be baseline value) at any time point during the Treatment Period. If the first measurement is during treatment (Study Drug End Day ≤ 2) then the confirmatory value can be post treatment. A single measurement > 5 × ULN followed by lost to follow-up also will be considered a confirmed (i.e., will not require confirmation). The concurrent elevation of post nadir ALT and total bilirubin will be determined by review of the listing which will include post nadir ALT > 3 × ULN and total bilirubin > 2 × ULN with direct bilirubin:total bilirubin ratio > 0.4.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality (if Applicable)

Vital sign variables are body temperature (oral), sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse rate, body weight, height, and waist circumference.

11.4.2 Statistical Methods

Vital signs will be summarized at each visit during the Treatment Period. The baseline value will be the last measurement on or before the day of the first dose of study drug. This same baseline value will be used for all change from baseline tables in the Treatment and Post-Treatment Periods.

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

12.0 References

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