1.0 Title Page

Statistical Analysis Plan

Study M14-423

An Open-Label, Multicenter Study to Evaluate Long-Term Outcomes With ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection

(TOPAZ-I)

Date: 22 March 2017

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by AbbVie Statistics and Statistical Programming for Study Protocol M14-423. TOPAZ-I (Study M14-423) and companion study TOPAZ-II (Study M14-222) are designed together and share the primary objective of assessing the effect of treatment response (assessed by SVR_{12} status, i.e., HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment) on long-term clinical outcomes in adults with genotype 1 (GT1) chronic hepatitis C virus (HCV) infection who received treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin, as measured by all-cause death, liver-related death, liver decompensation, liver transplantation, and hepatocellular carcinoma.

In the TOPAZ-I and TOPAZ-II studies, the primary objective is to assess the effect of treatment response on long-term clinical outcomes, based on the data from both studies combined. The studies differ based on geographic region (this study will be conducted outside the US while the TOPAZ-II study will be conducted in the US) and based on certain procedures that are not related to the primary outcome. For example, this study will assess the long-term change from baseline in liver elastography, and the TOPAZ-II study will utilize a Subject Care Plan Model to facilitate subjects' adherence to the study drug.

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 M14-423. 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 objective of this study is to evaluate the effect of virologic response to treatment (assessed by SVR_{12} status) on the long-term progression of liver disease in adults with chronic HCV GT1 infection who receive treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin, as measured by all-cause death, liver-related death, liver decompensation, liver transplantation, and hepatocellular carcinoma.

The secondary objectives are to evaluate the long-term progression of fibrosis and sustained virologic response in adults with GT1 chronic HCV infection who received treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin. Progression of fibrosis is measured by change from baseline in liver stiffness using transient elastography (FibroScan®), when available. Sustained virologic response is evaluated by the percentage of subjects achieving SVR_{12}.

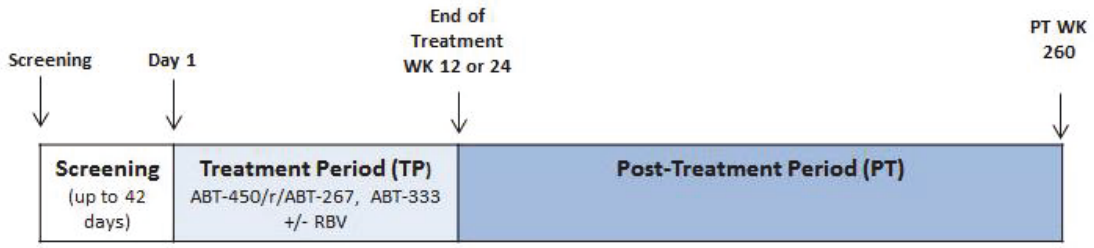
4.2 Design Diagram

Study M14-423 is a Phase 3b, open-label, multi-center study, which is designed together with companion Study M14-222 (TOPAZ-II) to share the primary objective of assessing the effect of treatment response on long-term clinical outcomes in adults with GT1 chronic HCV infection with or without compensated cirrhosis, who are either treatment-naïve or IFN/RBV (IFN or peg IFN/RBV) treatment-experienced. Approximately 1650 subjects will be enrolled in Study M14-423 at approximately 200 sites outside the US. The number of cirrhotic subjects (fibrosis stage of F4) will be limited to approximately 400 subjects; the number of subjects enrolled without fibrosis or with portal fibrosis without septa (fibrosis stage of F0 or F1) will be limited to approximately 1000 subjects.

As shown in Figure 1, subjects meeting eligibility criteria will be enrolled to either 12 or 24 weeks of treatment according to HCV subgenotype and presence of cirrhosis. Subjects

who receive at least one dose of study drug will be followed in the Post-Treatment Period for up to 5 years (PT Week 260).

Figure 1. Study Schematic



The duration of the study will be 272 weeks (for subjects receiving a 12-week treatment) or 284 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 260-week Post-Treatment (PT) Period for all subjects who receive at least one dose of study drug.

Treatment Period

Subjects who meet the eligibility criteria will be enrolled to either 12 or 24 weeks of combination therapy with or without RBV as described below and in Table 1.

All HCV GT1-infected subjects who are either treatment-naïve or treatment-experienced will receive ABT-450/r/ABT-267 150/100/25 mg once daily (QD) and ABT-333 250 mg twice daily (BID). Subjects with HCV GT1a infection and all GT1-infected subjects with compensated cirrhosis will also receive RBV with weight-based dosing 1000 or 1200 mg BID.

The treatment duration will be 12 weeks for all subjects except HCV GT1a-infected subjects with compensated cirrhosis, who will receive treatment for 24 weeks, unless a treatment duration of 12 weeks is selected by the investigator based on the subject's prior

treatment history. Subjects will receive a study drug regimen according to criteria listed in Table 1. Upon completing the Treatment Period or premature discontinuation of the Treatment Period, subjects will enter the Post Treatment (PT) Period.

Table 1. Treatment Regimen and Duration

Subject Population	Treatment Regimen*	Treatment Duration
Genotype 1a, without cirrhosis	ABT-450/r/ABT-267 + ABT-333 + ribavirin	12 weeks
Genotype 1a, with cirrhosis	ABT-450/r/ABT-267 + ABT-333 + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	ABT-450/r/ABT-267 + ABT-333	12 weeks
Genotype 1b, with cirrhosis	ABT-450/r/ABT-267 + ABT-333 + ribavirin	12 weeks

* Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

** Treatment for 12 weeks may be considered in some patients where consistent with the approved local label.

Post-Treatment Period

Subjects who receive at least one dose of study drug in the Treatment Period and either complete treatment or prematurely discontinue study drug will be followed in the Post-Treatment Period for up to 260 weeks. At the Post-Treatment visits, subjects will be assessed for antiviral response, progression of liver fibrosis, patient reported outcomes (PROs) and clinical outcomes, including all-cause death, liver-related death, and occurrence of hepatocellular carcinoma, liver decompensation and liver transplantation.

The Post-Treatment Period will begin the day following the last dose of study drug treatment.

4.3 Sample Size

Assuming 4% of subjects do not achieve SVR_{12} and assuming the 5-year event rate of the composite clinical outcome is 20% in the non-SVR_{12} subjects, with a 75% reduction in SVR_{12} subjects (Hazard Ratio of 0.25),[1,2] then based on two-sample log rank test (using EAST 6.0), a sample size of at least 2000 subjects enrolled in TOPAZ-I (planned to enroll 1650 subjects) and TOPAZ II (planned to enroll 600 subjects) provides greater than 80%

power to reject the null hypothesis of no difference between SVR_{12} and non-SVR_{12} subjects in the rate of clinical outcome events. Power calculations were based on a dropout rate of up to 20% for the hazard ratio.

4.4 Planned Analysis

The primary analysis to evaluate the effect of response to treatment on clinical outcomes, will occur at the final analysis after all subjects have completed the study or prematurely discontinued the study. An interim analysis to assess the percentage of subjects achieving SVR_{12} will occur after all subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinued the study. For both final and interim analyses, data will be locked after performing appropriate data cleaning. Data after the interim analysis will be added to a subsequent 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 the designee according to the methodologies specified in this SAP.

There is no intention of shortening the follow-up time of subjects based on efficacy findings from the interim analysis. The intention is to follow all subjects who receive study drug for 260 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 enrolled subjects in this study (ITT-I) and the companion study TOPAZ-II (ITT-II) who receive at least one dose of study drug.

The primary efficacy analysis on clinical outcomes will be performed on the ITT population.

5.1.2 Intention-to-Treat-I (ITT-I) Population

The ITT-I population will consist of all enrolled subjects in this study who receive at least one dose of study drug. The data from the ITT-I population will be presented for all subjects regardless of treatment duration and ribavirin use in one column.

All efficacy, patient reported outcomes and resistance analyses, except for the primary efficacy analysis, will be performed on the ITT-I population. In addition, sensitivity analyses of SVR_{12} will be performed on the Modified Intention-to-Treat-I Genotype (mITT-I-GT) population and Modified Intention-to-Treat-I Genotype and Virologic Failure (mITT-I-GT+VF) population, respectively, as specified in Section 10.6.

5.1.3 Safety Population

All subjects in this study who receive at least one dose of study drug will be included in the safety population. Safety analyses will be performed on the safety population and be presented also for all subjects together. In other words, the safety population will be the same as the ITT-I population.

Demographic and safety analyses will be performed on the safety population.

5.2 Variables Used for Stratification of Randomization

Approximately 1650 subjects will be enrolled to receive ABT-450/r/ABT-267 and ABT-333 with or without RBV depending on their HCV genotype and cirrhotic status. No stratification of randomization will be used for this study.

6.0 Analysis Conventions

ICON Inc is the central laboratory used in this study. The chemistry platform will be transitioned from the Roche Diagnostics Hitachi Modular System (old) to the Abbott Architecture (new) in January 2016 while the study is expected to be still on-going. The

chemistry data obtained from the old chemistry platform will be converted to the new chemistry platform and the converted data will be combined with the data obtained from the new system for all statistical analysis and the normal ranges associated with the new chemistry platform will be applied. The analysis of mean changes from baseline, shifts above and below the normal ranges, the flagging of potentially clinically significant (PCS) laboratory data, and the CTCAE grading of chemistry labs will be performed as if all the chemistry data were generated by one platform – the new chemistry platform.

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. 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 related 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 non-missing 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 non-missing 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 efficacy data are assigned to protocol-specified time points during the Treatment and PT Periods, respectively. All time points and corresponding time windows are defined based on the blood sample collection date.

For analyses of health-related quality of life (QoL) PROs collected throughout the study, the time windows specified in Table 4 will be used.

For laboratory data and vital signs, the time windows specified in Table 5 and Table 6 describe how data are assigned to protocol specified time points during the Treatment and PT Periods, respectively.

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]	1a	≤ 1[a]
Week 2	14	2 to 21
Week 4	28	22 to 56
Week 12	84	57 to 126
Week 24[b]	168	127 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. Week 24 Visit is only applicable to subjects assigned to 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 266
Post-Treatment Week 52	364	267 to 546
Post-Treatment Week 104	728	547 to 910
Post-Treatment Week 156	1092	911 to 1274
Post-Treatment Week 208	1456	1275 to 1638
Post-Treatment Week 260	1820	1639 to 2002
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 PRO Instruments

Scheduled Visit[a]	Nominal Day (Study Day)	Time Window (Study Days Range)
Day 1/Baseline	1[b]	≤ 1[b]
Week 4	28	2 to 56
Week 12	84	57 to 126
Week 24[c]	168	127 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 266
Post-Treatment Week 52	364	267 to 546
Post-Treatment Week 104	728	547 to 910
Post-Treatment Week 156	1092	911 to 1274
Post-Treatment Week 208	1456	1275 to 1638
Post-Treatment Week 260	1820	1639 to 2002
Final Post-Treatment Visit[e]		> 2 days after last dose of study drug

a. SF-36v2 and FACIT-F are collected at Baseline, Week 4, Week 12 and Week 24 (for subjects with 24 weeks of treatment), and Post-Treatment Weeks 4, 12, 24, 52, 104, 156, 208 and 260.

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.

Table 5. Laboratory Data and Vital Sign Visit Windows (Treatment Period)

Scheduled Time	Nominal Day (Study Day)	Time Window (Study Days Range)
Day 1/Baseline[a]	1	≤ 1
Week 2	14	2 to 21
Week 4	28	22 to 56
Week 12	84	57 to 126
Week 24[b]	168	127 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 on-treatment value. The upper bound of this Final window is Study Drug End Day ≤ 2.

Note: The result closest to the scheduled time point will be used. Data must also be ≤ 2 days of the last dose of study drug. Total Insulin is measured at baseline, Week 12, Week 24 (for subjects on 24-week treatment regimen only), or EOT, and will use those visit windows as defined above.

Table 6. Laboratory Data and Vital Sign Visit Windows (Post-Treatment Period)

Scheduled Time	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Days Range)
Post-Treatment Week 4	28	3 to 56
Post-Treatment Week 12	84	57 to 126
Post-Treatment Week 24	168	127 to 266
Post-Treatment Week 52	364	267 to 546
Post-Treatment Week 104	728	547 to 910
Post-Treatment Week 156	1092	911 to 1274
Post-Treatment Week 208	1456	1275 to 1638
Post-Treatment Week 260	1820	1639 to 2002
Final Post-Treatment Visit[a]		> 2 days after 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.

Note: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day > 2. Vital signs and hematology, chemistry, urinalysis, and coagulation panels are collected at every Post-Treatment Period visit. Urinalysis is not conducted after PT Week 4. Total Insulin is collected at Post-Treatment Weeks 52, 104, 156, 208, and 260 and will use those visit windows as defined above. FibroTest samples are collected at Post-Treatment Weeks 12 (or upon study discontinuation) and will use those visit windows as defined above.

6.3 Missing Data Imputation

No data will be imputed for any efficacy or safety analyses except for the PRO questionnaires, for analyses of the HCV RNA endpoints, and for analysis of the persistence of resistance. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. Similarly, the missing items of the FACIT-F questionnaire will be imputed with the average score of the answered items in the same scale as long as more than 50% (≥ 7 out of 13) of the items in the scale are answered. The SF-36v2 Mental and Physical Component Summary measures will not be computed if any domain is missing.

HCV RNA values will be selected for an SVR analysis based on visit windows as defined in Section 6.2. When there is no HCV RNA value in a visit window based on defined visit windows, the closest values before and after the window, regardless of the value chosen for the subsequent and preceding window, will be used for the flanking imputation described below.

If a subject has a missing HCV RNA value at a post-Day 1 visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and succeeding value, the HCV RNA level will be considered undetectable or unquantifiable, respectively, at this visit for this subject. In addition, if a subject has an unquantifiable HCV RNA level at the preceding value and an undetectable HCV RNA level at the succeeding value, or vice versa, the HCV RNA level will be imputed as unquantifiable at this visit for this subject. For SVR analyses, if there is no value in the appropriate window after flanking imputation but there is an HCV RNA value after the window, then it will be imputed into the SVR window. Subsequent to this flanking and backward imputation, if a subject is missing a value for the visit window associated with the analysis, the subject will be imputed as a visit failure (i.e., not undetectable or unquantifiable).

If a subject starts another treatment for HCV, then all HCV RNA and PRO assessment 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.

HCV RNA < LLOQ Analyses for SVR

If a subject is missing an HCV RNA value for the visit window associated with the analysis of SVR after performing the imputations described above, then this value will be imputed with an HCV RNA value from a local laboratory if present; otherwise, the HCV RNA value for this visit will be missing. Subjects with missing HCV RNA data in the analysis window, after imputations, will be imputed as a failure.

HCV RNA Analyses for Relapse and 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.

Finally, missing sequence data will be imputed as follows in the analysis of the persistence of resistance from the sequences from PT Week 52 through PT Week 260 (5 years). If a signature variant is not detectable by population, clonal or deep sequencing at PT Week 24 (or later), the variant is imputed as not detectable at the PT Week 52 (or timepoints after the sequence with the variant not detectable) and time points thereafter if a sample from Post-Treatment Week 52 or later is not sequenced. If a signature variant is detectable by population, clonal, or deep sequencing at Post-Treatment Week 52 or later, then the variant is imputed as being detectable at earlier time points if the sample at the earlier time point is not sequenced.

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

Demographics, baseline characteristics, medical history, and previous/concomitant medications will be summarized overall and by presence of cirrhosis and genotype 1 subtype on the safety population.

7.1 Demographic and Baseline Characteristics

Demographics include age, weight, height and BMI as continuous variables, and sex, race, ethnicity, age category ([< 55 years or ≥ 55 years] and [< 65 or ≥ 65 years]), birth year (< 1945, 1945 to 1965, > 1965), country, and BMI category (< 30 kg/m^2 or ≥ 30 kg/m^2).

Baseline characteristics will include: HCV genotype 1 subtype (1a, 1b, 1-other), IL28B genotype ([CC, CT, or TT] and [CC or non CC]), prior treatment history (treatment-naïve [IFN-eligible, IFN-ineligible] or IFN-based treatment-experienced [null responder, partial responder, relapser, prior relapse/breakthrough, prior nonresponder, IFN-intolerant and IFN experienced-other]), baseline HCV RNA levels ([continuous (use log_{10} HCV RNA)]

and [< 800,000 IU/mL or ≥ 800,000 IU/mL]), baseline HOMA-IR (< 3 or ≥ 3 mU × mmol/L^2), baseline fibrosis stage (F0 – F1, F2, F3, F4), baseline Child-Pugh score (non-cirrhotic, 5, 6, or > 6), baseline FibroTest score (continuous and [< 0.49, 0.49 – 0.58, 0.59 – 0.74, ≥ 0.75]), baseline albumin (continuous), baseline albumin (< 35, ≥ 35 g/L), baseline creatinine clearance (continuous; < 30 mL/min, ≥ 30 – 49 mL/min, ≥ 50 – 89 mL/min, ≥ 90 mL/min), baseline eGFR by MDRD (continuous; < 30, 30 – 59, 60 – 89, ≥ 90 mL/min/1.73 m^2; < 60 or ≥ 60 mL/min/1.73 m^2), baseline platelet count (continuous; < 90 × 10^9/L, ≥ 90 × 10^9/L; < 50 × 10^9/L, ≥ 50 × 10^9/L; < 100 × 10^9/L, ≥ 100 × 10^9/L; < 150 × 10^9/L, ≥ 150 × 10^9/L), baseline alpha fetoprotein (continuous, and < 20 ng/mL, ≥ 20 ng/mL), tobacco (user, ex-user, or non-user) and alcohol (drinker, ex-drinker, or non-drinker) use status, history of diabetes, history of depression or bipolar disorder, history of bleeding disorders, AST to platelet ratio index (APRI) (continuous; ≤ 2.0 or > 2.0), and Fibrosis-4 score (FIB-4) (continuous; ≤ 3.25, > 3.25).

Subjects' HCV genotype and subtype may be assessed based on the Inno-LiPA 2.0 Assay used by the Central lab, the ARUP Assay for Hepatitis C High-Resolution Genotype by the Central lab 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 HCV genotype and subtype. If it is not available, then the ARUP 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 ARUP 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 – F1, F2, F3, or F4.

For subjects with baseline fibrosis stage of F4, the baseline Child-Pugh score is determined by the Day 1 assessment of ascites and hepatic encephalopathy along with the baseline values of total bilirubin, serum albumin, and international normalized ratio (INR). The Child-Pugh score is the sum of the point assigned for each of the five observed findings as defined in Table 7.

Table 7. Child-Pugh Classification of Severity of Cirrhosis

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

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

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

Baseline APRI and FIB-4 are defined as the equations below. Subjects without baseline values of AST, platelet count or age will be excluded from the summary of APRI; subjects without baseline values of AST, ALT, platelet count, or age will be excluded from the summary of FIB-4.

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

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

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. Concomitant medications will be summarized for all subjects in the Safety population. 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, pegIFN and RBV) will be summarized separately from other prior medications.

Medications for the treatment of HCV will be collected in the PT Period 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

The number of subjects for each of the following categories will be summarized overall and by each investigator on the safety population.

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

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

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 interruptions and RBV dose modifications will be presented in the CSR listings.

9.0 Study Drug Exposure and Compliance

9.1 Exposure

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

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

At each protocol-specified visit, the total number of tablets dispensed and returned is recorded together for ABT-450/r/ABT-267 and ABT-333, and is recorded separately for RBV. The compliance for ABT-450/r/ABT-267 and ABT-333 combined and the compliance for RBV within the Treatment Period will be calculated as the percentage of tablets taken relative to the total tablets, respectively, expected to be taken. The total number of tablets prescribed will be equal to the total number of tablets that should have been taken per the protocol for the duration that the subject was in the Treatment Period (date of last dose – date of first dose + 1 day). Study drug interruptions due to an adverse event or other planned interruptions 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 tablets 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 summarized with the N, mean, SD,

median, minimum and maximum. In addition, the percentage of compliant subjects will be calculated separately for ABT-450/r/ABT-267 + ABT-333, and RBV.

10.0 Efficacy Analysis

10.1 General Considerations

The primary efficacy analysis on clinical outcomes will be performed on all subjects in the ITT population as defined in Section 5.1. All other efficacy analyses will be performed on the ITT-I population.

Treatment effects will be evaluated based on a two-sided significance level of 0.05 (when rounded to three decimal places). The data from the ITT-I population will be presented in one column/row as it represents the labelled treatment.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0. For this assay, the lower limit of quantification (LLOQ) and the lower limit of detection (LLOD) is 15 IU/mL. HCV RNA results that are detectable but not quantifiable are reported as "< 15 IU/mL" and results that are not detectable are reported as "NON-DETECTED."

Assessment of Clinical Outcomes

Incidence of the following clinical outcome events will be collected during the 12/24 weeks of treatment and the 5-year (PT Week 260) Post-Treatment Period. Data will be adjudicated by an independent outcome committee and results will be reported in the "Clinical Outcome" eCRFs:

- All-cause death: Death due to any cause.
- Liver-related death: Death as the result of a liver-related cause.
- Liver decompensation: Development of any of the following conditions: ascites, hepatic encephalopathy, or variceal bleeding.
- Liver transplantation: any subject who had a liver transplantation.

- Hepatocellular carcinoma (HCC): development of HCC in any subject at any time during the study. HCC is defined by histologic confirmation or a > 1 cm mass lesion on cross-sectional imaging that meets the diagnostic criteria for HCC according to EASL guidelines.
- Composite of any of the above outcomes.

Definitions for HCV RNA Efficacy Endpoints

Note that a confirmed quantifiable post-treatment value is defined as two consecutive post-treatment HCV RNA measurements ≥ LLOQ. During treatment, a confirmed quantifiable value is defined as any two consecutive HCV RNA values ≥ LLOQ, either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement.

Breakthrough = confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, 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 treatment. A single breakthrough value (≥ LLOQ or > 1 $\log_{10}$ IU/mL above nadir) followed by lost to follow-up will be considered a breakthrough (i.e., will not require confirmation).

On-treatment virologic failure = breakthrough or failure to suppress during treatment (all on-treatment values of HCV RNA ≥ LLOQ) with at least 6 weeks (defined as study drug duration ≥ 36 days) of treatment.

RVR (rapid virologic response) = HCV RNA < LLOQ in the Week 4 window.

EOTR (end of treatment response) = HCV RNA < LLOQ in the Week 12 window for subjects receiving 12 weeks of treatment and in the Week 24 window for subjects receiving 24 weeks of treatment.

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 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} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment.

$Relapse_{24}$ = confirmed HCV RNA ≥ LLOQ during SVR_{24} window among subjects who achieved SVR_{12} and have data available during the SVR_{24} window.

$Relapse_{late}$ = confirmed HCV RNA ≥ LLOQ at any time after the SVR_{24} assessment time point for a subject who achieved SVR_{24} and has post-SVR_{24} HCV RNA data available.

$Relapse_{overall}$ = 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 completes treatment. For relapse analyses, the completion of treatment is defined as a study drug duration ≥ 77 days for subjects assigned to 12 weeks of treatment and ≥ 154 days 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). Relapse analyses will exclude subjects who do not have any post-treatment HCV RNA values.

HCV re-infection 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. Re-infection 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 re-infection may be determined with a confirmed HCV genotype or subgenotype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Any subjects with documented re-infection will be excluded from relapse analyses and will be analyzed separately.

Reasons for SVR_{12} Non-Response

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

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. Relapse (defined according to the **$Relapse_{12}$** definition for subjects who complete treatment);
3. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{12} non-responder who prematurely discontinued study drug (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** definition);
4. Missing follow-up data in the SVR_{12} window [defined as any subject who completed study drug without data in the SVR_{12} window and not meeting the definitions of (1), (2), or (3)];
5. Other (including subjects with documented re-infections and subjects defined as any SVR_{12} non-responder not meeting the definitions of [1] – [4], such as a subject with a single quantifiable value within the SVR_{12} window followed by an undetectable value beyond the SVR_{12} window).

Reasons for SVR_{24} Non-Response

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

1. On-treatment virologic failure (see **On-treatment virologic failure definition**);
2. Relapse (defined according to the **$Relapse_{12}$** definition for subjects who complete treatment);
3. Relapsed after achieving SVR_{12} (see **$Relapse_{24}$**);
4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{24} non-responder who prematurely discontinued study drug and did not meet the **On-treatment virologic failure**, **$Relapse_{12}$**, or **$Relapse_{24}$** definitions);
5. Missing follow-up data in the SVR_{24} window [defined as any subject who completed study drug without data in the SVR_{24} window, and not meeting the definitions of (1), (2), (3), or (4)];
6. Other (including subjects with documented re-infections and subjects defined as any SVR_{24} non-responder not meeting the definitions of [1] – [5]).

10.2 Handling of Multiplicity

No adjustment for multiple comparisons is used in this open-label long-term outcome study.

10.3 Primary Efficacy Analysis

The primary efficacy analysis will be conducted among subjects in the ITT population as described in Section 5.1. HCV RNA values and SVR_{12} will be imputed as described in Section 6.3.

The primary efficacy endpoint is to assess the effect of response to treatment (as assessed by SVR_{12} status) on clinical outcomes by comparing the time to incidence of the following events between subjects who achieve SVR_{12} and those who do not.

- All-cause death
- Liver-related death
- Liver decompensation
- Liver transplantation
- Hepatocellular carcinoma
- Composite of any of the above outcomes

For each of the six event types as listed above, a subject's time to event will be defined as the number of days from the first day of study drug to the day the subject experiences an event of interest. All events of interest will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. However, events occurred after a subject started another treatment for HCV will be excluded and the subject will be censored at the time of starting the new HCV treatment. If the subject has not experienced an event of interest nor has the subject died (all-cause death), the subject's data will be censored at the date of the subject's last available assessment of clinical outcomes. All-cause death is a censoring event for liver-related death, liver decompensation, liver transplantation and hepatocellular carcinoma. For subjects with no post-baseline assessment, the subject's data will be censored on the first day of study drug. Time to the composite of clinical outcomes is the time to the first occurrence of any clinical outcome.

For each of the six event types, the distribution of time to event will be estimated for subjects who have achieved SVR_{12} and those who haven't using Kaplan-Meier methodology and compared between the subjects who have achieved SVR_{12} and those who haven't using the log-rank test.

For each of the six event types, the 1-, 2-, 3-, 4-, and 5-year event-free survival rate will be estimated using Kaplan-Meier methodology and a 95% confidence interval will be constructed separately for those who have achieved SVR_{12} and those who haven't.

For each of the six event types, a test statistic based on Kaplan-Meier estimates of the event-free survival probability at Year 5 and the estimated variance will be constructed to test the null hypothesis that the 5-year event-free survival rates for subjects who have achieved SVR_{12} and those who haven't are the same.

For each of the six event types, a Cox proportional hazards (PH) model will be constructed to include all the baseline characteristics as described in Section 7.1, SVR_{12} status, and other variables as appropriate to compare the risk of experiencing a clinical outcome between subjects who have achieved SVR_{12} and those who haven't.

10.4 Secondary Efficacy Analyses

The following analyses of secondary efficacy endpoints will be performed on the ITT-I population:

- The effect of sustained virologic response on change and percentage change from baseline in FibroScan score (assessed at the end of treatment and all post-treatment visits except PT Week 4) will be evaluated by comparing mean change from baseline at each applicable visit between subjects who achieve SVR_{12} and those who do not using descriptive statistics and ANCOVA analyses. SVR_{12} status will be included as a factor and baseline FibroScan score will be included as a covariate in the ANCOVA model. From the ANCOVA analyses, point estimates of the mean difference and 95% confidence intervals will be provided.
- Sustained virologic response will be evaluated using the percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The simple percentage of subjects achieving SVR_{12} will be calculated and a two-sided 95% confidence interval of the percentage will be computed based on Wilson's score method.

10.5 Efficacy Subgroup Analysis

The analysis on SVR_{12} rate as described in Section 10.4 will be performed on the ITT-I population for the following subgroups (assessed at baseline), as appropriate:

- The presence of cirrhosis and subgenotype (GT1b without cirrhosis, GT1b with compensated cirrhosis, GT1 non-b without cirrhosis, and GT1 non-b with compensated cirrhosis);
- Prior treatment history(treatment-naïve [IFN-eligible, IFN-ineligible] or IFN/RBV treatment-experienced [null responder, partial responder, relapser, prior relapse/breakthrough, prior nonresponder, IFN-intolerant and IFN experienced-other]);
- IL28B ([CC, CT, TT] and [CC or non-CC]);
- Sex (male or female);
- Age (< 55 or ≥ 55 years) and (< 65 or ≥ 65 years);
- Birth year (< 1945, 1945 to 1965, > 1965);
- Race (Black or Non-Black; Black will include any subject who marks 'Black or African American' for race on the Demographics eCRF);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- BMI (< 30 or ≥ 30 kg/m^2);
- Baseline HCV RNA levels (< 800,000 or ≥ 800,000 IU/mL; below median or above or equal to median);
- Baseline creatinine clearance (< 50 mL/min, ≥ 50 mL/min);
- Baseline eGFR by MDRD (< 30, 30 – 59, 60 – 89, ≥ 90 mL/min/1.73 m^2; < 60 or ≥ 60 mL/min/1.73 m^2);
- Baseline HOMA-IR (< 3 or ≥ 3 mU × $mmol/L^2$);
- History of Depression or Bipolar Disorder (yes/no);
- History of Bleeding Disorders (yes/no);
- Baseline Child-Pugh score (non-cirrhotic, 5, 6, or > 6);
- Baseline fibrosis stage (F0 – F1, F2, F3, F4);
- APRI (≤ 2.0 or > 2.0);

- FIB-4 (≤ 3.25 or > 3.25); Any of APRI > 2.0 and FIB-4 > 3.25, or neither.

For subjects with cirrhosis only:

- Baseline platelets (< 50×10^9/L, ≥ 50×10^9/L; < 90×10^9/L, ≥ 90×10^9/L; < 100×10^9/L, ≥ 100×10^9/L; < 150×10^9/L and ≥ 150×10^9/L);
- Baseline albumin (< 35, ≥ 35 g/L);
- Baseline alpha fetoprotein (< 20, ≥ 20 ng/mL);
- Any of platelets < 90×10^9/L, albumin < 35 g/L, or alpha fetoprotein ≥ 20 ng/mL, or none of the three.

The 2-sided 95% Wilson score confidence interval for a binomial proportion (percentage of subjects achieving SVR_{12}) will be produced for each subgroup with at least 10 subjects. In addition, stepwise logistic regression will be performed on both SVR_{12} and virologic failure (on-treatment virologic failure or relapse) using subgroup variables as described above. 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.

For GT1 non-b subjects with cirrhosis only:

- Treatment Duration (12 weeks, 24 weeks);

The analysis on liver stiffness (change and percentage change from baseline in FibroScan score) as described in Section 10.4 will be performed on the mITT-I-GT population for the following subgroup (assessed at baseline), as appropriate:

- The presence of cirrhosis (subjects with cirrhosis vs subjects without cirrhosis);

Subgroup analyses will be performed if there are an adequate number of subjects.

The effect of subgroup status on change and percentage change from baseline in FibroScan score (assessed at the end of treatment and all post-treatment visits except PT Week 4) will be evaluated if there are at least 10 subjects in each subgroup using summary statistics and ANOVA analyses separately for each applicable visit. The subgroup status, SVR_{12} status, and their interaction will be included in the model. From the ANOVA analyses, point estimates of the mean difference from the reference subgroup (subjects without cirrhosis) and 95% confidence intervals will be provided.

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

In addition to presenting the secondary efficacy endpoint of SVR_{12} as described in Section 10.4, two sensitivity analyses of SVR_{12} will be presented using the following modified populations. The first sensitivity analysis of SVR_{12} will be conducted using a Modified Intention-to-Treat Genotype (mITT-I-GT) population that includes subjects who receive at least 1 dose of study drug in Study M14-423 (with imputation as described in Section 6.3) but excludes the subjects who are not of HCV genotype 1 infection. The mITT-I-GT population is used to reduce the risk of bias that could occur due to enrolled population deviating from the protocol selected study population.

The other sensitivity analysis of SVR_{12} will be conducted using a Modified Intention-to-Treat Genotype and Virologic Failure (mITT-I-GT+VF) population. The mITT-I-GT+VF population is used to reduce the risk of bias that could occur due to either discordant HCV genotype or irrelevant failures unrelated to study drug. The mITT-I-GT+VF population includes all subjects who receive at least 1 dose of study drug in Study M14-423 (with imputation as described in Section 6.3) but excludes the subjects who are not of HCV genotype 1 infection and the subjects who did not achieve SVR_{12} due to reasons other than on treatment virologic failure or relapse.

10.7 Additional Efficacy Analyses

The following additional HCV RNA efficacy endpoints will be summarized and analyzed on the ITT-I population, as specified:

- The number and percentage of subjects with on-treatment virologic failure;
- The number and percentage of subjects with post-treatment relapse;
- The number and percentage of subjects with documented re-infection;
- The number and percentage of subjects with RVR;
- The number and percentage of subject with EOTR;
- The number and percentage with unquantifiable HCV RNA at each post-baseline visit throughout the Treatment Period (using data from the central laboratory as observed, i.e., no imputation for missing data);
- The number and percentage of subjects with HCV RNA < LLOQ 24 weeks after the last actual dose of study drug (SVR_{24});
- Reasons for not achieving SVR_{24} for subjects who do not;
- Mean change from baseline in prothrombin time (PT), International normalized ratio (INR), FibroTest, and albumin to each applicable post-baseline time point;
- The number of subjects who fail to suppress and accompanying listing;
- The number of subjects who breakthrough any time during treatment and accompanying listing;
- The number of completers with final on-treatment HCV RNA < LLOQ who relapse within the SVR_4 window, SVR_{12} window, or SVR_{24} window and accompanying listing;
- The concordance between SVR_{12} and SVR_{24} will be assessed.

In the above analyses that use the number and percentage of responders, 2-sided 95% Wilson score confidence interval for a binomial proportion will be calculated. Imputations for missing data will be performed as described in Section 6.3 for analyses of SVR, RVR, and EOTR, where a missing response will be imputed as a failure after performing the described imputation. All other endpoints will be presented using data as observed. For the change from baseline to each post-baseline time point in PT/INR, Fibrotest, and albumin, descriptive statistics will be calculated.

The number and percent of subjects who fail to suppress HCV RNA and received at least 6 weeks of treatment (active study drug duration ≥ 36 days) will be tabulated along with the subject numbers corresponding to the subjects who failed to suppress.

The number of subjects who breakthrough at any time during treatment and within each protocol-specified visit (defined in Table 2) will be summarized along with a corresponding listing displaying the subject numbers at the first occurrence of breakthrough.

The number of documented re-infected subjects who re-infected within the SVR_4 window, within the SVR_{12} window, within the SVR_{24} window (defined in Table 3), after the SVR_{24} window and anytime post-treatment (study drug end day ≥ 3) will be summarized along with a corresponding listing of the subjects numbers displaying the window of the first occurrence/detection of re-infection.

The number of completers (defined as study drug duration ≥ 77 days for subjects assigned to 12 weeks of treatment and ≥ 154 days for subjects assigned to 24 weeks of treatment) with final on treatment HCV RNA < LLOQ who relapse within the SVR_4 window, within the SVR_{12} window, within the SVR_{24} window (defined in Table 3), after the SVR_{24} window and anytime post-treatment (study drug end day ≥ 3) will be summarized along with a corresponding listing displaying the first occurrence of relapse. A similar table and listing will be provided of Preterm Relapses for subjects who do not complete treatment (defined as study drug duration < 77 days for subjects assigned to 12 weeks of treatment and < 154 days for subjects assigned to 24 weeks of treatment) with HCV RNA < LLOQ at the Final Treatment visit.

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}.

10.8 Resistance Analyses

If possible, subjects treated with study drug 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 next generation sequencing (NGS) 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 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; 56, 155, 156, and 168 in NS3 for genotype 1b; 2) for ABT-267: 28, 30, 31, 32, 58, and 93 in NS5A for genotype 1a; 28, 29, 30, 31, 32, 58, and 93 in NS5A for genotype 1b; 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, 558, 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 NGS in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on variant frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3, NS5A, or NS5B).
- Post-baseline variant by NGS: 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: A post-baseline variant or an enriched variant.

The following will be provided for subjects who are in the PVF population and have resistance data available.

Listings by subject of all baseline variants (≥ 2% and > 15% detection thresholds) relative to prototypic reference sequence at signature resistance-associated amino acid positions will be provided for each DAA target (NS3, NS5A, and NS5B).

A listing by subject of all baseline variants (≥ 15% detection threshold) at non-signature amino acid positions will be provided for each DAA target (NS3/4A, NS5A and NS5B).

A listing by subject and time point of all treatment-emergent variants relative to the baseline amino acid sequences will be provided across all DAA targets (NS3, NS5A, and NS5B).

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, 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 (1a or 1b) and DAA target (NS3, NS5A, or NS5B) and will list the subject numbers of subjects with each variant. The number of subjects with resistance variants in 3 targets, 2 targets or 1 target will be provided.

Listings by subject and time point of all post-baseline variants relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B). In addition, a listing by subject and time point of all post-baseline variants at signature resistance-associated amino acid positions relative to the appropriate prototypic reference amino acid sequences will be provided.

For all subjects who experience VF, the persistence of resistance-associated variants for each target (NS3, NS5A, and NS5B) will be assessed by NGS at Post-Treatment Weeks 24 and 52 and at time points up to Post-Treatment Week 260 (5 years). The number and percentage of subjects with post-baseline variants at signature amino acid positions, listed by amino acid position and variant within a DAA target at each Post-Treatment time point compared to baseline will be summarized, along with the number of subjects within a DAA target and overall. Additionally, the number and percentage of subjects in whom a signature variant persisted at Post-Treatment Week 24 and 52 and time points up to Post-Treatment Week 260 (5 years) out of the total number of subjects with that emerged variant at the VF time point and at that time point will be summarized by DAA target, and variant. The number and percentage of subjects who still have a variant at a given Post-Treatment time point will be calculated out of all subjects with that variant at VF who have sequencing at that time point. The imputation described below will be used for PT Week 52 or time points up to Post-Treatment Week 260 (5 years). If a

signature variant is not detectable at Post-Treatment Week 24, the variant is imputed as not detectable at the Post-Treatment Week 52 and time points thereafter even if a sample from Post-Treatment Week 52 or later is not sequenced. If a signature variant is detectable at Post-Treatment Week 52 or later, then the variant is imputed as being detectable at earlier time points even if the sample at the earlier time point is not sequenced.

If resistance-associated variants are not detected by NGS in a given target for a subject either at the time of failure or in a post treatment sample, then that target will not be sequenced in subsequent samples from that subject.

10.9 Patient Reported Outcomes

The following instruments will be used to collect patient reported outcomes (PROs): SF-36 version 2 (SF-36v2) and FACIT-F. Missing data for each measurement will be handled as described in Section 6.3.

The following exploratory analyses of PROs will be performed by baseline fibrosis stage:

- mean change from baseline to each applicable post-baseline time point in the SF-36v2 Mental Component Summary (MCS), Physical Component Summary (PCS) and eight individual domain measures;
- mean change from baseline to each applicable time point in the FACIT-F total score;
- percentage of subjects without a decrease from Baseline to Final Treatment Visit in the SF-36v2 PCS and MCS that is greater than or equal to the minimally important difference (MID) of five points.

The SF-36v2 measures dimensions of a patient's functional health and well-being in 8 domains and also provides 2 summary scores that characterize a patient's mental (MCS) and physical (PCS) health status. The score for each of the 8 domains ranges from 0 to 100 and will be normalized according to the user manual. The standardization of the normalized scores will provide the norm-based scores with a mean of 50 and a SD of 10.

The two summary scores are based on the norm-based scores. Per the SF-36v2 instrument manual, score for any item with multiple responses will be set to "missing." Subject's responses to the SF-36v2 will be summarized for the PCS and MCS measures.

The FACIT-F is a symptom specific instrument with a focus on measuring fatigue in a variety of chronic diseases or health conditions. Its 13-item-version assesses peripheral, central, or mixed fatigue and yields a summed total score ranging between 0 and 52. Higher FACIT-F scores indicate a lesser degree of fatigue. Notice that item 7 (I have energy) and item 8 (I am able to do my usual activities) are reverse scored.

Summary statistics (n, mean, SD, median, minimum and maximum) for the mean change from baseline to each applicable visit will be provided for the FACIT-F score and the SF-36v2 PCS and MCS scores.

In particular, an analysis of the mean change from baseline to Post-Treatment Week 12 and to Post Treatment Week 24 in the SF-36 V2 Vitality scale, Mental Component Summary score, Physical Component Summary score and FACIT-F score, will be performed using ANCOVA analyses with appropriate baseline fibrosis stage, SVR_{12} status, and their interaction as factors, and baseline PRO score as covariate. A summary of the analysis results comparing subjects who have achieved SVR_{12} and subjects who have not will be provided. A similar summary of analysis results comparing subjects with different fibrosis stage will be provided also. Additional analysis on the PRO data will be performed as useful and appropriate.

An MID of –5 will be used for the change from Baseline to Final Treatment Visit in the SF-36v2 PCS and MCS. The percentage of subjects with a change from Baseline to Final Treatment Visit > –5 will be presented along with 95% confidence intervals.

11.0 Safety Analysis

11.1 General Considerations

All subjects who receive at least one dose of study drug in Study M14-423 will be included in the safety analyses.

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;
- Severe treatment-emergent adverse events;
- 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;
- Moderate or severe treatment-emergent adverse events;
- Severe treatment-emergent adverse events;
- Grade 3 or 4 (see definition below) 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;
- 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 moderate to severe treatment-emergent adverse events and treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs.

Adverse Event of Special Interest

Specific treatment-emergent adverse events of special interest, which may be searched using Standardized or Company MedDRA Queries, will be summarized. The search criterion for the adverse event of interest is as follows:

- Hepatic Decompensation and Hepatic Failure
  PMQ "Hepatic decompensation and hepatic failure"

The number and percentage of subjects experiencing at least one treatment-emergent adverse event in the search for the event of interest will be presented by SOC and PT.

A listing of treatment-emergent adverse events for subjects meeting the search criterion will be provided for the adverse event of special interest.

Adverse Event by Maximum Severity

Treatment-emergent adverse events and treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs will be summarized by maximum severity of each preferred term. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity 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 adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

Adverse Events by Maximum Severity Grade Level

Treatment-emergent adverse events will be summarized by maximum severity grade level of each preferred term. Each preferred term will be assigned to a grade level based on severity and seriousness, adapted from the Division of AIDS (DAIDS) table for grading severity of adverse events. All serious adverse events will be categorized as Grade 4. Nonserious adverse events categorized by the investigators as mild, moderate, or severe will be categorized as Grade 1, Grade 2, or Grade 3, respectively. If a subject has a nonserious adverse event 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 adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Grade 3" category. Similarly, if a subject has an adverse event with unknown seriousness, then the subject will be counted in the severity grade level category of "unknown" unless the subject has another occurrence of the same adverse event that is marked serious. In this case, the subject will be counted under the "Grade 4" 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, PT/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), total insulin, creatinine clearance (Cockcroft-Gault calculation), calculation of estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD)

equation as defined below, alpha2-macroglobulin, haptoglobin, apolipoprotein A1, and alpha fetoprotein.

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

Additional variable is total insulin.

The following equation will be used to calculate eGFR by MDRD, where serum creatinine is measured in mg/dL and age is measured in years:

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

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	Very Low (VL)	Very High (VH)
Hemoglobin		
(mmol/L)	< 4.9	
(g/dL)	< 8.0	
(g/L)	< 80	
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

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
Magnesium		
(mmol/L)	< 0.4	> 1.23
(mg/dL)	< 0.9	> 3.0
Glucose		
(mmol/L)	< 2.2	> 13.9
(mg/dL)	< 40	> 250
Albumin		
(g/L)	< 20	
(g/dL)	< 2	

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

Test/Units	Very Low (VL)	Very High (VH)
Protein		
(g/L)	< 50	
(g/dL)	< 5.0	
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

Clinical laboratory tests 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 Period and Post-Treatment Periods.

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

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used in this study. Shift tables from baseline to minimum value, maximum value, and final values during the Treatment Period (Study Drug End Day ≤ 2) will be created. The shift tables will cross tabulate the frequency of subjects with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range.

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.

For hemoglobin and the liver function tests (LFTs) of alkaline phosphatase and total bilirubin, the number and percentage of subjects with a maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade of 1, 2, 3, or 4 (see definitions in Table 10) at any post-baseline visit (regardless of the baseline value) through the end of treatment (i.e., Final Treatment Value) will be summarized. All LFT tables will include summary rows for the number and percentage of subjects with at least Grade 2 and at least Grade 3 laboratory abnormalities. The hemoglobin table will include a summary row for the number and percentage of subjects with at least a Grade 2 laboratory abnormality.

For the liver function tests (LFTs) of ALT and AST, the number and percentage of subjects with a maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade of 1, 2, 3, or 4 (see definitions in Table 10) at any post-nadir visit (regardless of the baseline value) through the end of treatment (i.e., Final Treatment Value) will be summarized. Note, for these analyses, the nadir is used for reference instead of baseline. Both ALT and AST tables will include summary rows for the number and percentage of subjects with at least Grade 2 and at least Grade 3 laboratory abnormalities.

Accompanying listing of hemoglobin results will be provided for any subjects with at least Grade 2 hemoglobin abnormalities. Accompanying listings of all ALT, AST, total, indirect and direct bilirubin, and alkaline phosphatase will be created for any subject who had at least a Grade 3 ALT, AST, alkaline phosphatase, or total bilirubin. A listing of the hematology results will be provided for subjects with hemoglobin abnormalities.

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

The number and percentage of subjects meeting the following criteria will be summarized:

- ALT ≥ 3 × ULN and total bilirubin value ≥ 2 × ULN;
- ALT > 5 × ULN (equivalent to Grade 3 or higher) and total bilirubin value < 2 × ULN.

A subject or event will be counted if the post-nadir laboratory values meet the above criteria regardless of the baseline laboratory value (i.e., the post nadir laboratory value does not need to be worse than the baseline laboratory value). The maximum ratio relative to the ULN will be used to determine if subjects meet the criteria listed above.

For subjects meeting the ALT ≥ 3 × ULN and total bilirubin value ≥ 2 × ULN criterion during the Treatment Period, a corresponding listing of all ALT, AST, alkaline phosphatase, and total, direct, and indirect bilirubin values will be provided.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality (if Applicable)

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

Table 11. Criteria for Potentially Clinically Significant Vital Sign Values

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

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.

The number and percentage of subjects with post baseline values during the Treatment Period meeting Criteria for Potentially Clinically Significant Vital Sign Values (Table 11) will be summarized. A post-baseline value must be more extreme than the baseline value to be considered as a PCS finding. A separate listing will be provided that presents all of the vital sign values for the subjects meeting the PCS vital sign criteria during treatment.

12.0 References

1. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9(6):509-16.e1.
2. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147(10):677-84.
3. Julious SA. Two-sided confidence intervals for the single proportion: comparison of seven methods by Robert G. Newcombe, Statistics in Medicine. 1998;17:857-72. Stat Med. 2005;24(21):3383-4.
4. Cella D, Webster K. Linking outcomes management to quality-of-life measurement. Oncology (Williston Park). 1997;11(11A):232-5.
5. Ware JE Jr, Kosinski M, Bjorner JB, et al. User's Manual for the SF-36v2 Health Survey. 2nd ed. Lincoln, RI: QualityMetric Incorporated; 2007.