1.0 Title Page

Statistical Analysis Plan

Study M14-491

An Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267

(ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Treatment-Naïve and Treatment-Experienced Asian Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Compensated Cirrhosis

29 June 2016

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3.0 Introduction

This statistical analysis plan (SAP) for Study M14-491 is based on the study protocol dated 23 November 2015, incorporating Administrative Change 1. Study M14-491 examines the safety and efficacy of co-formulated ABT-450, ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 co-administered with ribavirin (RBV) for 12 weeks in adults with genotype 1b chronic hepatitis C virus (HCV) infection and compensated cirrhosis. Throughout the SAP, the combination of direct-acting antiviral agents (DAAs) with RBV, ABT-450/r/ABT-267 and ABT-333 plus RBV, will be denoted as "DAA combination regimen" for simplicity.

The protocol specifies that the primary analysis of efficacy (including resistance and Patient Reported Outcomes [PROs]) and safety data will occur after all subjects have completed the Post-Treatment Week 24 Visit or prematurely discontinued the study and that the primary analysis will summarize data collected through Post-Treatment Week 24. All remaining data through Post-Treatment Week 48 will be summarized in the end of study analysis.

Per agreement with the Center for Drug Evaluation (CDE)/China Food and Drug Administration (CFDA), an interim analysis that was not specified in the protocol will occur after all subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinued the study. This interim analysis will include analyses of SVR_{12} (HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following therapy), which is the primary endpoint for South Korea and Taiwan and the first element of the primary endpoints (SVR_{12} and SVR_{24}, HCV RNA < LLOQ 24 weeks following therapy) in the fixed-sequence testing procedure specified for China (see Section 10.2). The interim analysis will be conducted once SVR_{12} data for all subjects are available, rather than at the time specified in the protocol (i.e., once SVR_{24} data are available). The primary endpoints of the study for China (SVR_{12} and SVR_{24}), South Korea (SVR_{12}), and Taiwan (SVR_{12}) remain unchanged; only the timing of when SVR_{12} will be analyzed has changed. The interim analysis will allow each element of the primary endpoint to be

analyzed when data for the endpoint are available. Also, the hierarchy in the fixed-sequence testing procedure for the primary endpoints will be maintained. For these reasons, the Type I error rate for each primary endpoint will be preserved at 0.05. Furthermore, the interim analysis will not compromise the study integrity or results, will not affect the study sample size/power or study procedures, and will not pose a risk to subjects as subjects will have completed treatment at the time of the analysis. The interim analysis will include analyses of the endpoints specified in the protocol and this SAP for data collected through this time point. This interim analysis will support regulatory submission activities in China, South Korea, and Taiwan.

A previously planned interim analysis to support regulatory submission activities in South Korea and Taiwan was specified in the protocol. The planned interim analysis was to include all efficacy (including resistance and Patient Reported Outcomes [PRO]) and safety data through Post-Treatment Week 12 and was to occur after all subjects from South Korea and Taiwan completed the Treatment Period through Post-Treatment Week 12 or prematurely discontinued from the study. The planned interim analysis was not going to include hypothesis testing for the HCV RNA endpoints. The planned interim analysis will not be conducted, but will be replaced with the unplanned interim analysis, which will include hypothesis testing.

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. Analyses will be performed using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC) or a later version under the UNIX operating system.

Any deviations from the planned statistical analysis will be described and justified in the clinical study report, as appropriate.

This is the first version of the SAP for Protocol M14-491.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objectives of this study are to assess the safety and to compare SVR_{12} and SVR_{24} following 12 weeks of treatment with the DAA combination regimen to the historical SVR rate of telaprevir plus pegIFN and RBV therapy in HCV genotype 1b infected adults with compensated cirrhosis.

The secondary objectives of this study are to demonstrate the effect of the DAA combination regimen on HCV RNA levels during and after treatment as measured by on-treatment virologic failure and post-treatment relapse, respectively.

4.2 Design Diagram

This is a Phase 3, open-label, single-arm, multicenter study evaluating the efficacy and safety of the DAA combination regimen for 12 weeks in HCV genotype 1b, treatment-naïve and IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment-experienced adults with compensated cirrhosis.

The study is designed to enroll approximately 100 subjects (approximately 60 subjects from sites in China and 20 subjects each from sites in South Korea and Taiwan). At least 35 treatment naïve and 35 treatment-experienced subjects will be enrolled.

Treatment will consist of: ABT-450/r/ABT-267 150/100/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) + RBV* for 12 weeks.

* RBV will be administered weight-based 1000 – 1200 mg divided to twice daily.

The study consists of a Treatment Period and a Post-Treatment Period. During the Treatment Period, all enrolled subjects will receive 12 weeks of treatment. All subjects administered study drug will be followed for 48 weeks post-treatment to test for durability of SVR and emergence or persistence of DAA resistance associated variants. The duration of the study will be 60 weeks, not including a screening period of up to 35 days.

Treatment Period

Subjects meeting eligibility criteria will be enrolled via Interactive Response Technology (IRT) and will receive ABT-450/r/ABT-267 orally QD and ABT-333 with RBV orally BID. Subjects will be administered the first doses of study drugs at the site on Study Day 1.

Post-Treatment Period

All subjects who receive at least one dose of DAA in the Treatment Period and either complete treatment or prematurely discontinue study drug will be monitored in the Post-Treatment Period for safety, HCV RNA, the emergence and persistence of resistant viral variants and assessment of PROs for an additional 48 weeks following the last dose of study drug.

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

4.3 Sample Size

It is planned to enroll approximately 100 subjects (60 from China, 20 from South Korea and 20 from Taiwan). With a total sample size of about 100 subjects and assuming that 94% of the subjects will achieve SVR_{12}, this study has greater than 90% power to demonstrate SVR_{12} superiority with a 2-sided 95% lower confidence bound greater than 67% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 6.2). The SVR_{24} rate is anticipated to be very similar to the SVR_{12} rate and thus the power should still be at least 90%. No adjustment for dropout is applicable because subjects who do not have data at Post-Treatment Week 12 and Post-Treatment Week 24 (after imputing) are counted as failures for SVR_{12} and SVR_{24}, respectively.

4.3.1 Justification of Primary Endpoint Success Criteria

The current study is an Asian study examining the combination of ABT-450/r/ABT-267 and ABT-333 administered with RBV for 12 weeks in treatment-naïve and IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment-experienced HCV genotype 1b-infected subjects with compensated cirrhosis. This is a similar trial design as in AbbVie Study M13-099. In Study M13-099, the SVR_{12} rate for each treatment arm was compared to an historical SVR rate for telaprevir plus pegIFN and RBV (54%, see Table 1). A weighted average of the corresponding SVR rates among treatment-naïve and treatment-experienced (prior relapsers, partial responders and null responders) in HCV genotype 1 infected cirrhotic subjects was calculated to reflect the population expected to enroll in Study M13-099. The historical rate of 54% was defined conservatively as the upper bound of the 95% confidence interval for the telaprevir-based rate.

Table 1. Estimated SVR Rates for Telaprevir Plus PegIFN and RBV in Cirrhotic Subjects

	Telaprevir-Treated Subjects with Cirrhosis n/N (%)	Projected Enrollment in Study M13-099 (%)	Population-Based Weighted Average % [95% CI]
Meta Analysis of ADVANCE[1] and ILLUMINATE[1] Studies			
Naïve Subjects	(56)	53	
REALIZE[1]			
Prior relapsers	48/57 (84)	12	47 [41, 54]
Prior partial responders	11/32 (34)	12	
Prior null responders	7/50 (14)	23	

Consistent with Study M13-099, the SVR_{12} and SVR_{24} rates from the current study will be compared to a clinically relevant threshold based on historical SVR rates for telaprevir plus pegIFN/RBV. However, since the historical SVR rate used in Study M13-099 is based on a population that included HCV genotype 1a-infected cirrhotic subjects as well as HCV genotype 1b-infected cirrhotic subjects, a higher threshold will be used in this study to account for a genotype 1b only population.

Because data are not available on the subpopulation of HCV genotype 1b-infected subjects with cirrhosis treated with telaprevir plus pegIFN/ RBV, the SVR rates in HCV genotype 1a and genotype 1b-infected, non-cirrhotic subjects treated with telaprevir plus pegIFN/RBV were used to determine an appropriate adjustment factor to increase the historical rate used in Study M13-099. An appropriate adjustment factor was determined based on the relative failure rate between the HCV genotype 1b and genotype 1a populations in the telaprevir ADVANCE, ILLUMINATE, and REALIZE studies (Table 2 and Table 3). For treatment-naïve subjects, the SVR failure rate in genotype 1b subjects was reduced by a relative 29% (from 28% to 20%) from the SVR rate for genotype 1a subjects (Table 2). For treatment-experienced subjects, the SVR failure rate in genotype 1b was also reduced by a relative 29% (from 41% to 29%) from the SVR rate for genotype 1a subjects (Table 3). Since the SVR rate for the genotype 1a cirrhotic subjects is not available and SVR rate for all cirrhotic patients would be higher than that for genotype 1a cirrhotic subjects, it would be more conservative to estimate the SVR rate for the genotype 1b cirrhotic subjects by taking 29% reduction from the combined data from genotype 1a + genotype 1b cirrhotic subjects together. Therefore, to account for the exclusion of HCV genotype 1a-infected subjects in the current study, the historical SVR failure rate of 46% used in Study M13-099 for genotype 1 was reduced by a relative 29%, resulting in a 33% failure rate (or 67% SVR rate) for genotype 1b. The rate of 67% should be conservative because the 54% was based on a population that was a mix of genotype 1a and 1b and the expectation is that the SRV rate for genotype 1a subjects would be lower than the SVR rate for the mix population of genotype 1a and 1b subjects. Hence, for this current study, for a regimen to be considered superior to a clinically meaningful threshold based on SVR rates for telaprevir plus pegIFN/RBV, the lower confidence bound of the SVR rate must exceed 67%. The value of 67% used for the superiority comparison represents the 54% historical genotype 1 SVR rate plus a relative 29% adjustment factor for the exclusion of genotype 1a subjects.

Table 2. SVR Rates for Telaprevir Plus pegIFN and RBV Therapy in Treatment-Naïve Subjects by Subgenotype

	ADVANCE	ILLUMINATE	Meta Analysis
Telaprevir Studies	**T12/PR n/N (%)**	**T12/PR n/N (%)**	**T12/PR % [95% CI]**
Treatment-Naïve GT1a Subjects	162/217 (75)[1]	273/388 (70)[2]	72 [68, 75]
Treatment-Naïve GT1b Subjects	119/145 (84)[1]	112/149 (75)[3]	80 [75, 84]

CI = confidence interval; GT1a = genotype 1a; GT1b = genotype 1b

Table 3. Estimated SVR Rates for Telaprevir-Based Therapy in Treatment-Experienced Subjects by Subgenoytpe

	REALIZE[†‡]				
	GT1a (Pooled T12/PR48) n/N (%)	**With Increase for Excluding Cirrhotics (%)**	**GT1b (Pooled T12/PR48) n/N%**	**With Increase for Excluding Cirrhotics (%)**	**Population-Based Weighted Average* % [95% CI]**
Relapse	119/142 (83.8)	84.3	123/140 (87.9)	88.4	GT1a 59 [53, 65]
Partial responders	26/55 (47.3)	59.3	27/40 (67.5)	79.5	GT1b 71 [64, 77]
Null responders	24/88 (27.3)	36.5	22/59 (37.3)	46.5	

CI – confidence interval; GT1a = genotype 1a; GT1b = genotype 1b

† US Prescribing Information for INCIVEK™ (telaprevir). Vertex Pharmaceuticals Incorporated; Cambridge, MA.

‡ Zeuzem S, Andreone P, Pol S, et al. REALIZE trial final results: telaprevir-based regimen for GT1 hepatitis c virus infection in patients with prior null response, partial response or relapse to peginterferon/ribavirin. J Hepatol. 2011;54 Suppl:S3.

* Based on a population of 30% relapsers, 35% partial responders, 35% null responders.

Furthermore, as the primary endpoints combine data from the three geographical regions (China, South Korea, and Taiwan), it was necessary to set one threshold for each primary endpoint.

In general, the SVR rate for telaprevir/pegIFN/RBV is greater than that of the standard of care of pegIFN/RBV in each of the geographic regions participating in this study. Additionally, this regimen has demonstrated superiority to pegIFN/RBV in a global Phase 3 program. The reported SVR rates for pegIFN/RBV vary significantly from report to report and are different in each of the 3 geographic regions. The SVR rates for telaprevir/pegIFN/RBV are 80% in cirrhotic and non-cirrhotic treatment-naïve GT1b-infected patients and 69% to 71% in cirrhotic and non-cirrhotic treatment-experienced GT1a-infected patients.[4] In China, South Korea, and Taiwan the pegIFN/RBV SVR rates range from 10% to 44%,[5] 20.8%[6] and 60.7%,[7] respectively. Therefore, AbbVie believes that demonstrating the superiority of the DAA combination regimen to the SVR with telaprevir/pegIFN/RBV will ensure the superiority of the DAA combination regimen to the SVR achieved locally with pegIFN/RBV treatment. However, as sensitivity analyses (see Section 10.5), comparisons of the SVR_{12} and SVR_{24} rates will be made to geographic region-specific SVR rates with pegIFN/RBV treatment as appropriate.

4.4 Planned Analysis

The primary analysis of SVR_{24} data will occur after all subjects have completed the Post-Treatment Week 24 Visit or prematurely discontinued the study. All remaining data through Post-Treatment Week 48 will be summarized in the end of study analysis.

For each analysis specified above, the data will be locked after performing appropriate data cleaning.

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

4.5 Unplanned Interim Analysis

An interim analysis that was not specified in the protocol will occur after all subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinued the study. This interim analysis will include SVR_{12}, which is the primary endpoint for South Korea and Taiwan and the first element of the primary endpoints (SVR_{12} and SVR_{24}) in the fixed-sequence testing procedure specified for China (see Section 10.2). The interim analysis will be conducted once SVR_{12} data are available, rather than at the time specified in the protocol (i.e., once SVR_{24} data are available). The primary endpoints of the study for China (SVR_{12} and SVR_{24}), South Korea (SVR_{12}), and Taiwan (SVR_{12}) remain unchanged; only the timing of when SVR_{12} will be analyzed has changed. The interim analysis will allow each element of the primary endpoint to be analyzed when data for the endpoint are available. Also, the hierarchy in the fixed-sequence testing procedure for the primary endpoints will be maintained. For these reasons, the Type I error rate for each primary endpoint will be preserved at 0.05. Furthermore, the interim analysis will not compromise the study integrity or results, will not affect the study sample size/power or study procedures, and will not pose a risk to subjects as subjects will have completed treatment at the time of the analysis. The interim analysis will include analyses of the endpoints specified in the protocol and this SAP for data collected through this time point. This interim analysis will support regulatory submission activities in China, South Korea, and Taiwan.

For the interim analysis, the data will be locked after performing appropriate data cleaning. Data collected after this lock will be added to a new version of the database. All analyses will be conducted by statisticians or programmers at AbbVie (or their designees) 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 48 weeks following treatment. There will be no statistical adjustment employed due to the interim analysis.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Intent-to-Treat (ITT) Population

All enrolled subjects who receive at least one dose of study drug will be included in the ITT population. The ITT Population will be used for efficacy, PROs, and resistance analyses.

Modified Intent-to-Treat (mITT) Populations

Sensitivity analyses of SVR_{12} and SVR_{24} will be performed on the modified ITT – Genotype (mITT – GT), modified ITT – Genotype and SVR_{12} Virologic Failure (mITT – GT + VF_{SVR12}), and modified ITT – Genotype and SVR_{24} Virologic Failure (mITT – GT + VF_{SVR24}) populations as specified in Section 10.5.

The mITT-GT population includes subjects who receive at least 1 dose of study drug but excludes the subjects who do not have HCV genotype 1b infection. The mITT-GT population is used to reduce the risk of bias that could occur due to the enrolled population deviating from the population intended to be treated with the regimen assigned in this study.

The mITT-GT + VF_{SVR12} and mITT-GT + VF_{SVR24} populations include all subjects who receive at least 1 dose of study drug but excludes the subjects who do not have HCV genotype 1b infection and the subjects who were not categorized as virologic failures (i.e., on-treatment virologic failure or non-infection relapse by Post-Treatment Week 12 for mITT-GT + VF_{SVR12}, and on-treatment virologic failure or non-infection relapse by Post-Treatment Week 24 for mITT-GT + VF_{SVR24}). The mITT-GT + VF_{SVR12} and mITT-GT + VF_{SVR24} populations are used to reduce the risk of bias that could occur due to either discordant HCV genotype or failures unrelated to study drug.

Safety Population

All enrolled subjects who receive at least one dose of study drug will be included in the Safety Population. Demographics, baseline characteristics, medical history, previous/concomitant medications, subject disposition, exposure, compliance, and safety analyses will be performed on the Safety Population, unless otherwise noted. The Safety Population will be the same as the ITT Population.

5.2 Variables Used for Stratification of Randomization

There is no randomization for this study.

6.0 Analysis Conventions

6.1 Definition of Baseline and Final Values

Definition of Baseline

The baseline value refers to the last non-missing measurement collected before the first dose of study drug is received. All assessments, except for HCV RNA, on Study Day 1 should be performed prior to administering the first dose of study drug per protocol. The baseline value is therefore determined by the last non-missing measurement collected on or before the first day of study drug administration. For HCV RNA, samples will be collected on Day 1 prior to dosing and 2 hours after dosing. Therefore, the baseline HCV RNA value will be determined by the last non-missing measurement collected prior to dosing.

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 the 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.

Definition of Study Days (Days Relative to the First Dose of Study Drug)

Study Days are calculated for each time point in the Treatment Period 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.

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

For all subjects who receive at least one dose of study drug, study drug end days 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.

Definition of 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.

Definition of 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 Definition of Analysis Windows

For efficacy analyses of HCV RNA and resistance, the time windows specified in Table 4 and Table 5 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.

The visit windows used for analyses of health-related quality of life (QoL) patient reported outcomes (PROs) collected throughout the study are described in Table 6.

For laboratory data and vital signs, the time windows specified in Table 7 describe how data are assigned to protocol-specified time points.

Except for analyses of SVR (e.g., SVR_4, and SVR_{12}), 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. For analyses of SVR, 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 4. Analysis Time Windows for HCV RNA and Resistance Endpoints (Treatment Period)

Scheduled Visit	Nominal Day/ Time (Study Day)	Time Window (Study Days Range)
Baseline[a]	--	≤ 1[a]
Week 1	7	2 to 10
Week 2	14	11 to 21
Week 4	28	22 to 35
Week 6	42	36 to 49
Week 8	56	50 to 63
Week 10	70	64 to 77
Week 12	84	78 to 98
Final Treatment Visit[b]	2 to ≤ 2 days after last dose of study drug	
$SVR_{12planned}$[c]	168	141 to 210
$SVR_{24planned}$[c,d]	252	211 to 294

a. HCV RNA values on Day 1 must also be before the time of the first study drug administration.

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

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

d. Not included in interim analysis.

Note: Except for Final Treatment Visit and SVR windows, the result closest to the scheduled time point (nominal day/time) will be used. For visits through Week 12, data must also occur before or on Study Drug End Day 2.

Table 5. Analysis Time Windows for HCV RNA and Resistance Endpoints (Post-Treatment Period)

Scheduled Visit	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Days Range)
Post-Treatment Week 2	14	3 to 21
Post-Treatment Week 4	28	22 to 42
Post-Treatment Week 8	56	43 to 70
Post-Treatment Week 12	84	71 to 126
Post-Treatment Week 24[a]	168	127 to 210
Post-Treatment Week 36[a]	252	211 to 294
Post-Treatment Week 48[a]	336	295 to 378
SVR_4	28	3 to 56
SVR_{12}	84	57 to 126
SVR_{24}[a]	168	127 to 210

a. Not included in interim analysis.

Note: For Post-Treatment visits the results closest to the scheduled time point (nominal day) will be used. For SVR windows the last value in the window will be used. For all windows, the data must also occur after Study Drug End Day 2.

Table 6. Analysis Time Windows for PRO Instruments

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Days Range)
Day 1/Baseline[a]	1	≤ 1
Week 4	28	2 to 42
Week 8	56	43 to 70
Week 12	84	71 to 98
Final Treatment Visit[b]	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[c]	168	127 to 252
Post-Treatment Week 48[c]	336	253 to 378
Final Post-Treatment Visit[d]	> 2 days after last dose of study drug	

a. A value is considered to be baseline if it is the last non-missing value on or before Study Day 1.

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

c. Not included in interim analysis.

d. 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 Post-Treatment Visit window is Study Drug End Day 3 with no upper bound.

Note: Except for Final Treatment Visit and Final Post-Treatment Visit, the result closest to the scheduled time point (nominal day) will be used. For visits through Week 12, data must also occur before or on Study Drug End Day 2. For Post-Treatment visits, data must also occur after Study Drug End Day 2 for all windows.

Table 7. Laboratory Data and Vital Sign Visit Windows

Scheduled Visit	Nominal Day/Time (Study Day)	Time Window (Study Days Range)
Day 1/Baseline[a]	1	≤ 1
Week 1	7	2 to 10
Week 2	14	11 to 21
Week 4	28	22 to 35
Week 6	42	36 to 49
Week 8	56	50 to 63
Week 10	70	64 to 77
Week 12	84	78 to 98
Final Treatment Visit[b]	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 2	14	3 to 21
Post-Treatment Week 4	28	22 to 42
Post-Treatment Week 8	56	43 to 70
Post-Treatment Week 12	84	71 to 126
Post-Treatment Week 24[c]	168	127 to 210
Post-Treatment Week 36[c]	252	211 to 294
Post-Treatment Week 48[c]	336	295 to 378
Final Post-Treatment Visit[c]	> 2 days after last dose of study drug	

a. A value is considered to be baseline if it is the last non-missing value on or before Study Day 1.

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

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 Post-Treatment Visit window is Study Drug End Day 3 with no upper bound.

Notes: Except for Final Treatment Visit and Final Post-Treatment Visit, the result closest to the scheduled time point will be used. For visits through Week 12, data must also occur before or on Study Drug End Day 2. For Post-Treatment visits, data must also occur after Study Drug End Day 2 for all windows.

IP-10 is measured at Baseline, Weeks 4, 8, and 12, PT Week 12, and PT Week 48. Total Insulin is measured at Baseline and Week 12. Child-Pugh classification is collected at Screening, Week 12, and PT Week 12. Clinical assessments of ascites and hepatic encephalopathy for calculation of Child-Pugh classification are collected on Day 1 prior to dosing. FibroTest samples are collected at Baseline, PT Week 12, and PT Week 48. Analyses of these variables will use the visit windows as defined above.

6.3 Missing Data Imputation

Data will be imputed for HCV RNA analyses of RVR, EOTR, and SVR and for analyses of PRO questionnaires.

HCV RNA

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

For the flanking imputation, if a subject has a missing HCV RNA value at a post-baseline visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and the succeeding value, then the HCV RNA level will be imputed as 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 analyses of RVR, subjects still missing a value for the visit after flanking imputation will be imputed as a failure. For analyses of SVR, subjects still missing visit values after flanking imputation will have backward imputation applied. 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 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.

HCV RNA < LLOQ Analyses for RVR, EOTR, and SVR

If a subject is missing an HCV RNA value for the visit window associated with the analysis of RVR, EOTR, or 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 failures.

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.

PRO Questionnaires

If more than 4 items of the 16-item HCV-PRO are missing responses, then the total score is set to missing. When four or fewer items are missing, the mean of the non-missing items will be used to impute the responses for the missing item(s) and a total score will be calculated.

For EQ-5D-5L, no imputation will be performed for missing items.

For SF-36 Health Survey version 2, if a respondent answers at least 50% of the items in a multi-item scale of SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. The Mental and Physical Component measure will not be computed if any domain is missing.

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

Demographics, baseline characteristics, medical history and previous/concomitant medications will be summarized by geographic region (China, South Korea, Taiwan) and

overall for all subjects in the safety population and all subjects in the mITT-GT and mITT-GT+VF populations, if applicable.

7.1 Demographic and Baseline Characteristics

Demographics include age, weight, and body mass index (BMI) as continuous variables, and sex, race, ethnicity, type of Asian descent (Chinese, Korean, or Taiwanese), geographic region (China, South Korea, or Taiwan), age category (< 55 or ≥ 55 years; < 65 or ≥ 65 years), BMI category (< 30 or ≥ 30 kg/m^2), and women of childbearing potential (females between the ages of 18 and 55 years, inclusive [yes or no]).

Baseline characteristics will include prior IFN-based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment history (treatment-naïve or treatment-experienced; non-responder [null responder, partial responder, or other non-responder], relapser, or IFN-based therapy intolerant), IL28B genotype (CC, CT, or TT; CC or non-CC), screening HCV RNA (≤ 1000, > 1000 to 10,000, or > 10,000 IU/mL), baseline $\log_{10}$ HCV RNA level (continuous), baseline HCV RNA level (< 800,000 or ≥ 800,000 IU/mL), baseline IP-10 (continuous; < 600 or ≥ 600 ng/L), baseline HOMA-IR (< 3 or ≥ 3 mU × $mmol/L^2$), Child-Pugh score at Screening (5 or 6), baseline Child-Pugh score (5, 6, or > 6), baseline longitudinal FibroTest score (continuous), baseline platelet counts (continuous; < 60, 60 to < 90, 90 to < 120, or ≥ 120 × 10^9/L), baseline albumin (continuous; (< 28, 28 to < 33, 33 to < 40, 40 to 49, or > 49 g/L; < 35 or ≥ 35 g/L), baseline alpha fetoprotein (continuous), presence of hepatic steatosis at baseline (yes or no), hepatoprotective drug use at baseline (yes or no), tobacco and alcohol use status (current, former, never), former injection drug user (yes, no, or unknown), stable opiate substitution use (yes or no), history of bleeding disorders (yes or no), history of diabetes (yes or no), history of depression or bipolar disorder (yes or no), history of hypertension (yes or no), and history of cardiovascular disease (yes or no).

If the IL28B genotype result is not available from a sample collected during the Screening period, then a result available from a sample collected at any time during the study will be

used to summarize IL28B genotype. IL28b rs12979860 will be resulted as C/C, C/T, T/T, or Unable to Assign Genotype by the central laboratory.

HOMA-IR is defined as fasting glucose (mmol/L) × fasting insulin (μIU/mL) ÷ 22.5. Subjects who do not have a fasting glucose value and/or a fasting insulin value at Baseline will be excluded from the summary of baseline HOMA-IR.

Histories of diabetes, depression or bipolar disorder, bleeding disorders, hypertension, and cardiovascular disease will be based on the Medical History (MH) eCRF. History of diabetes is defined as presence of "Metabolic/Diabetes mellitus" on the MH eCRF. History of depression or bipolar disorder is defined as presence of "Neurologic and Psychiatric System/Depression" or "Neurologic and Psychiatric System/Bipolar Disorder" on the MH eCRF. All medical history terms within "Clotting/bleeding problems" or "Other" under the "Blood" body system on the MH eCRF will be reviewed to identify subjects with a history of bleeding disorders (e.g., hemophilia). History of hypertension is defined as presence of "Cardiovascular/Hypertension" on the MH eCRF. History of cardiovascular disease is defined as conditions or diagnoses of "Angina," "Myocardial infarction," "Congestive heart failure," and "Coronary artery disease" under the "Cardiovascular" body system. Medical history terms within "Other Body System" or any condition/diagnosis of "Other" may be reviewed for all baseline characteristics determined by the MH eCRF.

Baseline Child-Pugh score is calculated using the Day 1 assessment of ascites and hepatic encephalopathy along with the baseline values of total bilirubin, serum albumin, and INR. The Child-Pugh score is the sum of the points assigned for each of the five observed findings as defined in Table 8. Child-Pugh score at all other visits will be based on the total score automatically calculated on the eCRF.

Table 8. 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.

Subjects' HCV genotype and subtype may be assessed based on the Inno-LiPA 2.0 Assay used by the Central laboratory 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 Inno-LiPA 2.0 assay result will be used to categorize the subject.

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

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 calculated. 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

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

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

8.0 Subject Disposition

Disposition data will be summarized for the set of all subjects in the safety population overall and separately for each geographic region.

The number of subjects for each of the following categories will be calculated overall and by investigator:

- Subjects enrolled to this study;
- Subjects who took at least one dose of study drug;
- Subjects who completed study drug;
- Subjects who discontinued from study drug;
- Subjects who discontinued from the study;
- Subjects who completed the study;
- Subjects ongoing in the Post-Treatment Period at the time of the primary analysis.

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

A table that lists reasons for discontinuation of study drug will be provided for women of childbearing potential who discontinued study drug.

The number and percentage of subjects will be calculated 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 eGFR;
  - 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 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

9.1 Exposure

The duration of exposure to study drug will be summarized for the set of all subjects in the safety population and for each geographic region (China, South Korea, Taiwan). 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, standard deviation, median, minimum, and maximum) will be presented. Study drug duration also will be summarized with frequencies and percentages using the following categories: 1 to 15 days, 16 to 30 days, 31 to 45 days, 46 to 60 days, 61 to 75 days and > 75 days.

9.2 Compliance

At each protocol-specified visit during the Treatment Period, the total number of tablets dispensed and returned is recorded for each type of study drug. The compliance for each study drug (ABT-450/r/ABT-267, ABT-333, and RBV) within the Treatment Period will be calculated as the percentage of tablets taken relative to the total tablets expected to be taken. The total number of tablets 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 study drug for each subject in the safety population and summarized with the N, mean, median, standard deviation, minimum, and maximum for each geographic region (China, South Korea, Taiwan) and overall. In addition, the percentage of compliant subjects will be calculated for each study drug by geographic region and overall.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

Efficacy analyses will be performed on the ITT population, unless otherwise noted.

Missing data will be imputed as described in Section 6.3 for analyses of the HCV RNA endpoints of RVR, EOTR and SVR and the PRO questionnaires. Except for the local laboratory imputation for RVR, EOTR and SVR that is described in Section 6.3, HCV RNA values will be limited to those obtained from the central laboratory.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v. 2.0. For this assay, the lower limit of quantification (LLOQ) is 15 IU/mL. HCV RNA results that are detectable but not quantifiable are reported as "< 15 IU/ML HCV RNA DETECTED" and results that are not detectable are reported as "NO HCV RNA DETECTED."

Definitions for 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.

Failure to suppress = never achieved HCV RNA < LLOQ during at least 6 weeks of treatment (study drug duration ≥ 36 days).

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

On-treatment virologic failure = rebound 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.

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.

$SVR_{12planned}$ = HCV RNA < LLOQ in the $SVR_{12planned}$ window (12 weeks after the last planned dose of study drug [i.e., Week 24]) 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. This will not be included in the interim analysis.

$SVR_{24planned}$ = HCV RNA < LLOQ in the $SVR2_{4planned}$ window (24 weeks after the last planned dose of study drug [i.e., Week 36]) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window. This will not be included in the interim analysis.

$Relapse_4$ = confirmed HCV RNA ≥ LLOQ between end of treatment and 4 weeks after last actual dose of study drug (up to and including the SVR_4 assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment.

$Relapse_{12}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment.

$Relapse_{24}$ = 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. This will not be included in the interim analysis.

$Relapse_{late}$ = 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. This will not be included in the interim analysis.

$Relapse_{overall}$ = 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. 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 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 subtype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0.

Post-treatment non-reinfection relapse is defined as relapse was described earlier ($Relapse_4$, $Relapse_{12}$, $Relapse_{24}$, $Relapse_{late}$, $Relapse_{overall}$), but with 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 non-reinfection relapse unless an HCV genotype or subgenotype switch is confirmed by the Versant HCV Genotype Inno-LiPA Assay v2.0.

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) with further breakdown by non-reinfection relapse versus reinfection;
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) 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 after applying the imputation rules and not meeting the definitions of [1], [2], or [3]);

5. Other (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 (Not Included in the Interim Analysis)

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. $Relapse_{12}$, with further breakdown by non-reinfection relapse versus reinfection;
3. $Relapse_{24}$, with further breakdown by non-reinfection relapse versus reinfection;
4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{24} non-responder who prematurely discontinued study drug (duration < 77 days) 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 after applying the imputation rules and not meeting the definitions of [1], [2], [3], or [4]);
6. Other (defined as any SVR_{24} non-responder not meeting the definitions of [1] – [5]).

10.2 Handling of Multiplicity

Because of local regulatory requirements in China, both SVR_{12} and SVR_{24} are specified as primary endpoints. In order to control the Type I error rate at 0.05, a fixed-sequence testing procedure[8] will be used to proceed through the primary endpoints specified for China in the order numbered below for each. That is, for China, only if success has been demonstrated for the primary endpoint of superiority of the SVR_{12} rate to the historical

rate (B1) will the testing continue to the second primary endpoint of superiority of the SVR_{24} to the historical rate (B2) specified in Section 10.3.

For South Korea and Taiwan, only SVR_{12} is specified as a primary endpoint. Therefore no multiplicity adjustment will be made.

10.3 Primary Efficacy Analysis

For South Korea and Taiwan the primary endpoint is:

A1. SVR_{12}: Superiority to the historical SVR rate for telaprevir plus pegIFN/RBV therapy; the lower confidence bound (LCB) of the 95% CI for the percentage of subjects with SVR_{12} must exceed 67% to achieve superiority.

For China, the primary endpoints are:

B1. SVR_{12}: Superiority to the historical SVR rate for telaprevir plus pegIFN/RBV therapy; the LCB of the 95% CI for the percentage of subjects with SVR_{12} must exceed 67% to achieve superiority.

B2. SVR_{24}: Superiority to the historical SVR rate for telaprevir plus pegIFN/RBV therapy; the LCB of the 95% CI for the percentage of subjects with SVR_{24} must exceed 67% to achieve superiority.

For China, in order to control the Type I error rate at 0.05, a fixed-sequence testing procedure will be used to proceed through the primary efficacy endpoints as specified in Section 10.2.

To test the hypothesis that the percentage of treatment-naïve and IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) treatment-experienced HCV genotype 1b infected Asian subjects with compensated cirrhosis treated with the DAA treatment regimen for 12 weeks who achieve SVR_{12} is superior to a clinically meaningful threshold based on the historical SVR rates for the HCV genotype 1 infected population treated with telaprevir plus pegIFN/RBV, the percentage of subjects with SVR_{12} will be calculated with a 2-sided 95% CI using the Wilson score method,[9] and the LCB will be compared to the

defined threshold. The LCB of the 95% CI of SVR_{12} must be greater than 67% in order for the regimen to be considered superior.

Similarly, to test the hypothesis that the percentage of treatment-naïve and IFN based therapy treatment-experienced HCV genotype 1b infected Asian subjects with compensated cirrhosis treated with the DAA treatment regimen for 12 weeks who achieve SVR_{24} is superior to a clinically meaningful threshold based on historical SVR rates for the HCV genotype 1 infected population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR_{24} will be calculated with a 2-sided 95% CI using the Wilson score method, and the LCB will be compared to the defined threshold. The LCB of the 95% CI of SVR_{24} must be greater than 67% in order for the regimen to be considered superior.

The value of 67% used in the endpoints as the historical SVR rate for telaprevir plus pegIFN/RBV is described in Section 4.3.1.

10.4 Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment virologic failure during the Treatment Period;
- The percentage of subjects with post-treatment relapse (defined as $Relapse_{12}$), with further breakdown by non-reinfection relapse versus reinfection based on HCV population sequencing;
- The percentage of subjects with relapse by Post-Treatment Week 24 (confirmed HCV RNA ≥ LLOQ between end of treatment and 24 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment), with further breakdown by non-reinfection relapse versus reinfection based on HCV population sequencing.

The percentages (with two-sided 95% confidence intervals using the Wilson score method) of the subjects with virologic failure during treatment and post-treatment relapse will be calculated.

10.5 Sensitivity Analyses for the Primary Efficacy Endpoint

Sensitivity analyses of the primary endpoints specified in Section 10.3 using the imputation methods described in Section 6.3 will be performed by geographic region on the ITT population and by geographic region and overall on the mITT-GT population, the mITT-GT + VF_{SVR12} population, and the mITT-GT + VF_{SVR24} population defined in Section 5.1.

Additionally, the percentage of subjects achieving SVR_{12} and SVR_{24} will be summarized for the ITT population by geographic region and overall using the following alternative imputation methods to impute missing post-treatment virologic results:

- Impute as described in Section 6.3 but exclude subjects who were categorized for SVR_{12} (or SVR_{24}) non-response as "prematurely discontinued study drug with no on-treatment virologic failure," "missing follow-up data in the SVR_{12} (or SVR_{24}) window" or "other;"
- Impute any missing HCV RNA values in the SVR_{12} (or SVR_{24}) window by carrying forward the last non-missing (post-baseline) HCV RNA value prior to the SVR_{12} (or SVR_{24}) window;
- no imputation such that all missing HCV RNA values will be treated as failures;
- impute as described in Section 6.3 but exclude local laboratory HCV RNA data.

An additional sensitivity analysis will be performed for SVR_{12} and SVR_{24} in which the LLOQ will be replaced with 25 IU/mL; this analysis will be performed by geographic region and overall for the ITT population.

For each of these, the simple percentage of subjects with SVR_{12} (or SVR_{24}) will be presented along with a two-sided 95% CI using the Wilson score method.

As a sensitivity analysis, comparisons of the SVR_{12} and SVR_{24} rates will be made to geographic region-specific SVR rates with IFN based therapy (IFN with RBV). The rates of 44% from China, 20.8% from South Korea, and 60.7% from Taiwan will be used for comparisons (references provided in Section 4.3). The SVR_{12} and SVR_{24} rates for the overall ITT population will be compared to each of these rates, and the SVR_{12} and SVR_{24} rates for the ITT population from each geographic region will be compared to the geographic region-specific IFN-based therapy rate.

10.5.1 Assessment of Homogeneity Across Geographic Regions

Heterogeneity across the three geographic regions will be examined for the primary efficacy endpoints of SVR_{12} and SVR_{24} using the chi-square test of homogeneity. The three strata are China, South Korea, and Taiwan.

A confidence interval based on a stratum-weighted variance will be calculated using the equations below. The variance of p_s will be estimated by:

$$Var(p_s) = \sum_{h=1}^{H} W_h^2 \frac{p_h(1-p_h)}{N_h - 1}$$

and the 2-sided 95% confidence interval will be calculated as $p_s \pm z \sqrt{Var(p_s)}$, where z is the 1-α/2 point of the standard normal distribution. Note that N represents the number of subjects in the ITT population, N_h represents the number of subjects in stratum h, $W_h = N_h/N$, p_h = the proportion of subjects achieving SVR_{12} (or SVR_{24}) in stratum h, and p_s = the proportion of subjects with SVR_{12} (or SVR_{24}) among N subjects, which can be defined as:

$$p_s = \sum_{h=1}^{H} W_h p_h$$

10.6 Additional Efficacy Analyses

As additional efficacy analyses, the secondary endpoints will also be summarized for each geographic region (China, South Korea, Taiwan).

The following additional efficacy endpoints will be summarized on the ITT population by geographic region and overall.

- mean change from baseline in FibroTest score to each applicable post-baseline time point.
- the percentage of subjects 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 percentage of subjects with "failure to suppress;"
- the number of subjects with virologic rebound at each protocol-specified visit in the Treatment Period;
- the percentage of subjects with RVR;
- the percentage of subjects with EOTR;
- time to suppression of HCV RNA (defined as the study day of the first occurrence of HCV RNA < LLOQ) during the Treatment Period;
- the percentage of subjects achieving SVR_4;
- the percentage of subjects with $Relapse_4$, with further breakdown by non-reinfection relapse versus reinfection based on HCV population sequencing;
- the percentage of subjects achieving $SVR_{12planned}$;
- the percentage of subjects achieving $SVR_{24planned}$;
- the percentage of subjects with $Relapse_{24}$, with further breakdown by non-reinfection relapse versus reinfection based on HCV population sequencing;
- the percentage of subjects with $Relapse_{late}$, with further breakdown by non-reinfection relapse versus reinfection based on HCV population sequencing;
- the percentage of subjects with $Relapse_{overall}$, with further breakdown by non-reinfection relapse versus reinfection based on HCV population sequencing;

- time to relapse at any time post-treatment (defined in text below with additional relapse analyses);

For the change from baseline to each post-baseline time point in FibroTest score, descriptive statistics (N, mean, SD, median, minimum, and maximum) will be calculated.

For HCV RNA virologic response, the number and percentage of subjects with RVR, EOTR, SVR, on-treatment virologic failure, and post-treatment relapse will be calculated along with two-sided 95% confidence intervals using the Wilson score method; missing data will be imputed as described in Section 6.3. All other endpoints will be presented using data as observed, i.e., not performing any missing data imputations.

The number and percentage of subjects who do not achieve SVR_{12} (or SVR_{24}) by reason for non-response (defined in Section 10.1) will be calculated, and the non-responders will be presented in a listing.

The subjects who fail to suppress HCV RNA and received at least 6 weeks of treatment (study drug duration ≥ 36 days) will be presented in a listing. The subjects who rebound at any time during treatment and within each protocol-specified visit (defined in Table 4) will be presented in a listing displaying the subject numbers at the first occurrence of breakthrough.

The number of completers (defined as study drug duration ≥ 77) with final on-treatment HCV RNA < LLOQ who relapse at any time post-treatment and within each SVR window will be calculated 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) with HCV RNA < LLOQ at Final Treatment Visit. These summaries will include data collected after Post-Treatment Week 12.

From HCV RNA levels, the time to relapse post-treatment will be calculated for each subject treated with study drug and displayed graphically using a Kaplan-Meier (KM)

curve. For time to relapse analyses, time to event will be measured as the number of days from the last dose of active study drug to event or censoring time. The time of relapse post-treatment is defined as the first of two consecutive HCV RNA values ≥ LLOQ between the end of the treatment period and end of the Post-Treatment Period amongst subjects who completed study drug with HCV RNA < LLOQ at the Final Treatment Visit. Subjects who do not relapse will be censored at the date corresponding to the last available HCV RNA value within the Post-Treatment Period. Time to relapse will be performed only for subjects with HCV RNA < LLOQ at Final Treatment Visit who completed study drug, defined as a study drug duration ≥ 77 days.

The time to suppression on treatment will be calculated for each subject treated with study drug and displayed graphically using a KM curve. For time to suppression analyses, time to event will be measured as the number of days from the first dose of study drug to event or censoring time. The time of suppression is defined as the first occurrence of HCV RNA values < LLOQ during a treatment period. Subjects who do not suppress will be censored at the date of the last HCV RNA value within the corresponding treatment period.

The concordance between SVR_{12} and SVR_{24} will be assessed by the agreement between SVR_{12} and SVR_{24} and by the positive predictive value (PPV) and negative predictive value (NPV) of SVR_{12} on SVR_{24}. The agreement between SVR_{12} and SVR_{24} is a percentage defined as the number of subjects achieving both SVR_{12} and SVR_{24} and the number of subjects 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 did not achieve SVR_{12}.

10.7 Efficacy Subgroup Analysis

Analyses will be performed for the primary efficacy variables of SVR_{12} and SVR_{24} on the ITT population by geographic region (China, South Korea, Taiwan) and overall using the following subgroups:

- Previous HCV treatment status (Treatment-naïve versus previous IFN-based therapy [IFN (alpha, beta or pegIFN) with RBV] treatment-experienced;
  - For treatment-experienced subjects, type of response to previous IFN-based therapy (non-responder, relapser, or IFN-based therapy intolerant);
  - For non-responders to previous IFN-based therapy, type of response (null responder, partial responder, or other non-responder);
- IL28B genotype (CC or non-CC) and (CC, CT, or TT);
- Sex (male or female);
- Age (< 55 or ≥ 55 years) and (< 65 or ≥ 65 years);
- BMI (< 30 or ≥ 30 kg/m^2);
- Baseline HCV RNA level (< 800,000 or ≥ 800,000 IU/mL);
- Baseline IP-10 (< 600 or ≥ 600 ng/L);
- Baseline HOMA-IR (< 3 or ≥ 3 mU × $mmol/L^2$);
- Baseline Child-Pugh Score (5, 6 or > 6);
- Baseline platelets (< 90 or ≥ 90 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline alpha fetoprotein [AFP] (< 20 or ≥ 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;
- RBV dose modifications (yes/no);
- History of Depression or Bipolar Disorder (yes/no);
- History of Diabetes (yes/no);
- History of Bleeding Disorders (yes/no);
- Presence of hepatic steatosis at Baseline (yes/no);
- Hepatoprotective drug use at Baseline (yes/no);

- Former injection drug use (yes/no).

The numbers and percentages of subjects achieving SVR_{12} and SVR_{24} within each subgroup will be provided. If there are 10 or more subjects within the subgroup level, then a two-sided 95% confidence interval will be calculated using the Wilson score method.

A logistic regression model will be used to explore the associations between the subgroup variables and SVR_{12} (or SVR_{24}) on all subjects in the ITT population. A stepwise logistic regression approach will be used to assess the strength of each subgroup variable in predicting SVR_{12} (or SVR_{24}), with *P* values of 0.10 to enter and remain in the model. Subgroup variables may be changed to be continuous to prevent separation. A similar analysis will be performed to explore the associations between each of the subgroup variables and virologic failure (on treatment virologic failure or $Relapse_{12}$ for SVR_{12}; on treatment virologic failure or $Relapse_{12}$ or $Relapse_{24}$ for SVR_{24}).

10.8 Resistance Analyses

If possible, subjects who do not achieve SVR_{12} (or SVR_{24}) will have resistance testing conducted if (1) they have on-treatment rebound; (2) they have a study drug duration $\geq$ 77 days and then experience post-treatment relapse; or (3) they have at least 6 weeks of treatment and fail to suppress by Week 6. Subjects meeting one of these criteria will be considered to have experienced virologic failure and will be referred to as subjects in the primary virologic failure (PVF) population; a listing by subject that includes reason for SVR_{12} (or SVR_{24}) 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 reason for SVR_{12} (or SVR_{24}) 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 $\leq$ 1000 IU/mL).

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo population sequence analysis in order to allow accurate assessment of the products of amplification. For subjects who experience virologic failure, the sample closest in time after failure with an HCV RNA level ≥ 1000 IU/mL will be used if the HCV RNA level at the time of failure is < 1000 IU/mL. The prototypic reference strain with its associated GenBank Accession ID for sequence analyses is 1b-Con1 (AJ238799).

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 in genotype 1b are 1) for ABT-450: 55, 56, 155, 156, and 168 in NS3; 2) for ABT-267: 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93 in NS5A; and 3) for ABT-333: 316, 368, 411, 414, 445, 448, 553, 556, 558, and 559 in NS5B.

The following definitions will be used in the resistance analyses:

- Baseline sample: sample collected before the first dose of DAA study drug.
- 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 by population sequencing.

For those samples evaluated, a listing by subject of all baseline variants relative to the prototypic reference sequence at signature resistance-associated amino acid positions will be provided for each DAA target (NS3, NS5A, and/or NS5B). Furthermore, the HCV amino acid sequence at post-baseline time points with an HCV RNA level of ≥ 1000 IU/mL that are analyzed will be compared to the baseline and 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 for each DAA target (NS3, NS5A, and/or 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 prototypic reference amino acid sequences will be provided. Furthermore, the number and percentage of subjects with emerged variants by amino acid position and variant within a DAA target as compared to baseline will be summarized.

The persistence of resistance-associated substitutions that emerged for each target (NS3, NS5A, and NS5B) will be assessed by population sequencing at selected post-treatment time points. 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). The analysis of any resistance data from samples collected after Post-Treatment Week 24 will be summarized in the end of study analysis.

10.9 Patient Reported Outcomes

The following instruments will be used to collect patient reported outcomes (PROs): HCV-PRO, EQ-5D-5L, and SF-36 version 2 (SF-36v2). PROs will be collected at protocol-specified visits for all enrolled subjects. The HCV-PRO, EQ-5D-5L, and SF-36v2 will be collected at Baseline, Weeks 4, 8, and 12, and Post-Treatment Weeks 4, 12, 24 and 48, or upon premature discontinuation of the Treatment or Post-Treatment Periods. Missing data for each instrument will be handled as described in Section 6.3. PROs will be summarized on the ITT population by geographic region (China, South Korea, Taiwan) and overall.

The following analyses of PROs will be performed:

- mean change from baseline in HCV-PRO total score to each applicable post-baseline time point;
- mean change from baseline in EQ-5D-5L health index score and VAS score to each applicable post-baseline time point;

- mean change from baseline to each applicable post-baseline time point in the SF-36v2 Mental Component Summary (MCS) and Physical Component Summary (PCS) measures;
- continuous plots of the change from Baseline to Final Treatment Visit and PT Week 12 in the SF-36v2 PCS and MCS, HCV-PRO total score, EQ-5D-5L health index score and VAS on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis;
- 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;
- percentage of subjects without a decrease from Baseline to Final Treatment Visit in the EQ-5D-5L health index score that is greater than or equal to its study-defined MID;
- percentage of subjects without a decrease from Baseline to Final Treatment Visit in the HCVPRO total score that is greater than or equal to its study-defined MID.

The HCV-PRO consists of 16 items with 5 response choices (1, 2, 3, 4, or 5) that are recoded to 0, 1, 2, 3, or 4, respectively, when deriving the total score. The total score is the sum of all 16 items and is converted to a score between 0 and 100 by *ScaledScore=Sum*100/64*. Subject's responses to the self-administered HCV-PRO instrument will be assessed for the total score. Subject's responses to the EQ-5D-5L 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-5L 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).[10,11] The VAS score will be measured separately. The SF-36v2 measures dimensions of a patient's functional health and well-being in 8 domains and also provides 2 summary scores that characterize a patient's mental (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.[12] 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." Missing item responses will be handled as described in Section 6.3. Subject's responses to the SF-36v2 will be summarized for the PCS and MCS measures.

Summary statistics (n, mean, SD, median, minimum and maximum) for the mean change from baseline to each applicable visit will be provided for the HCV-PRO total score, EQ-5D-5L index and VAS scores, and the SF-36v2 PCS and MCS scores.

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.

To calculate the MID for HCVPRO and EQ-5D-5L, a receiver operating characteristics (ROC) analysis will be performed from PROC LOGISTIC with each of the following anchors for the change from Baseline to Final Treatment Visit in the HCVPRO total score and in the EQ-5D-5L health index score:

- Change from Baseline to Final Treatment Visit in SF-36 PCS > –5 [yes/no];
- Change from Baseline to Final Treatment Visit in SF-36 MCS > –5 [yes/no].

Change from Baseline to Final is defined as the Final Score – Baseline Score within the Treatment Period for all subjects in the ITT population. The point on the ROC curve that is closest to the upper left-hand corner (0, 1) yields the optimal sensitivity and specificity. This point will be determined by minimizing $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$. The cutoff point corresponding to the sensitivity and specificity values closest to (0, 1) for each anchor will be averaged and used as the MID. The MID determined for the HCV-PRO total score will be used for the change from baseline to Final Treatment Visit in HCV-PRO total score. The MID determined for the EQ-5D-5L health index score will be used for the change from baseline to Final Treatment Visit in EQ-5D-5L health index score. The percentage of subjects in each treatment group with a change from Baseline to Final Treatment Visit > MID will be presented along with 95% confidence intervals. If, for example, the MID is determined to be –10 for the HCVPRO total score, then the

responders are subjects with an improvement from baseline and subjects with decreases between zero and 10 points in the change from Baseline to Final Treatment Visit in HCV-PRO total score.

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will be performed on the safety population. For analyses of safety, data will be summarized by geographic region (China, South Korea, and Taiwan) and for the overall set of subjects.

11.2 Analysis of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Any worsening of a pre-existing condition or illness is considered an AE. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) with the MedDRA version used for the study at the time of database lock. The actual version of the MedDRA coding dictionary will be noted in the study report.

11.2.1 Treatment-Emergent Adverse Events

A treatment-emergent AE is defined as any AE with an onset date that is after the first dose of study drug and no more than 30 days after the last dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment emergent, unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

11.2.1.1 Tabulations of Treatment-Emergent Adverse Events

AE data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs). The SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC. Subjects reporting more than one AE for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one AE within a SOC will be counted only once for that SOC. Subjects reporting more than one AE will be counted only once in the overall total.

Adverse Event Overview

An overview of 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 AE 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;
- Moderate or severe treatment-emergent adverse events;
- Serious 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 modification;
- 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");
- Deaths (any event after the first dose of study drug, regardless of how many study days after the last dose of study drug).

Adverse Events by SOC and PT

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

- Treatment-emergent adverse events;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs;
- 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 modification;
- 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").

A listing of treatment-emergent adverse events grouped by SOC and PT with subject numbers will be created.

Adverse Events by PT

The number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to PT and sorted by overall frequency. Similar summaries will be provided for moderate to severe treatment-emergent adverse events and treatment emergent adverse events with a "reasonable possibility" of being related to DAAs and RBV.

Adverse Events of Special Interest

Specific treatment-emergent adverse events of special interest, which will be searched using Standardized or Company MedDRA Queries, will be summarized. The search criteria for each of the adverse events of interest are summarized in Table 9.

Table 9. Adverse Events of Special Interest

Adverse Event of Special Interest	Search Criteria
Hepatotoxicity-related events	SMQ "Drug-related hepatic disorders – severe events only" (broad search)
Bilirubin-related events	SMQ "Cholestasis and jaundice of hepatic origin" (broad search)
Anemia	SMQ "Haematopoietic erythropenia" (broad search) plus the following preferred terms: • Haemolytic anaemia, • Coombs negative haemolytic anaemia, • Coombs positive haemolytic anaemia
Drug-induced rash events	CMQ "Drug induced rash" (latest CMQ version based on MedDRA version used at time of analysis)
Severe cutaneous reactions	SMQ "Severe cutaneous adverse reactions" (narrow search)

For each adverse event of interest, 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 each adverse event of special interest.

Adverse Events 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 PT. 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 PT. Each PT 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 and does not have another occurrence of the same event that is marked serious or severe, then the subject will be counted in the severity grade level category of "unknown," even if the subject has another nonserious occurrence of the same event with a severity present. If the subject has another occurrence of the same adverse event with the most extreme severity for nonserious events ("Severe") and does not have another occurrence of the same event that is marked serious, then the subject will be counted under the "Grade 3" category. If the subject has another occurrence of the same adverse event that is marked serious, then the subject will be counted under the "Grade 4" category.

Adverse Events by Maximum Relationship

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

11.2.2 Listings of Adverse Events

The following listings of adverse events will be prepared:

- All serious adverse events (from the time the subject signed the study-specific informed consent through the end of the study);
- Treatment-emergent serious adverse events;
- Treatment-emergent adverse events leading to death;
- Treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent adverse events leading to study drug interruption;
- Treatment-emergent adverse events leading to RBV dose modification;
- Treatment-emergent adverse events in each of the adverse events of special interest categories.

11.3 Analysis of Laboratory Data

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses.

11.3.1 Variables and Criteria Defining Abnormality

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

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, 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 (Cockcroft-Gault calculation), calculation of estimated glomerular

filtration rate (eGFR) adjusted for the Asian population using the Chinese modification of diet in renal disease (C-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 (reflex performed if other variables are abnormal).

Additional variables include: total insulin and IP-10.

The following calculation is used by the central lab for eGFR by C-MDRD, where serum creatinine is measured in mg/dL and age is measured in years:

eGFR (mL/min/1.73 m^2) = 175 × Serum $Creatinine^{(-1.234)}$ × $Age^{(-0.179)}$ × 0.79 (if Female).

The Criteria for Potentially Clinically Significant (PCS) Laboratory Findings are described in Table 10 and Table 11.

Table 10. Criteria for Potentially Clinically Significant Hematology Values

Test/Units (if applicable)	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 11. Criteria for Potentially Clinically Significant Chemistry Values

Test/Units (if applicable)	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		≥ 2.0 × ULN
Creatinine		
(mcmol/L)		≥ 132.605
(mg/dL)		≥ 1.5
Creatinine Clearance (mL/min)	< 50	
eGFR using C-MDRD (mL/min/1.73 m^2)	< 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 11. Criteria for Potentially Clinically Significant Chemistry Values (Continued)

Test/Units (if applicable)	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 protocol-specified visit. 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 Period.

At each protocol-specified post-baseline visit, including applicable post-treatment visits, protocol-specified hematology, clinical chemistry, insulin, IP-10, and urinalysis pH and specific gravity parameters will be summarized with the baseline mean; visit mean; and change from baseline mean, standard deviation, minimum, maximum, 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 Period meeting the specified criteria for Potentially Clinically Significant (PCS) laboratory values (defined in Table 10 and Table 11) will be calculated. 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 laboratory values for the subjects meeting PCS criteria during treatment.

Hemoglobin and the liver function tests (LFTs) of ALT, AST, alkaline phosphatase, and total bilirubin will be assigned a CTCAE Grade of 1, 2, 3, or 4 as defined in Table 12. The number and percentage of subjects with a maximum CTCAE Grade of 1, 2, 3 or 4 at any post-baseline visit during the Treatment Period (regardless of the baseline value) will be calculated. All LFT summaries will also include the number and percentage of subjects with at least a Grade 2 and at least a Grade 3 laboratory abnormality. The hemoglobin table will include a summary row for the number and percentage of subjects with at least a Grade 2 laboratory abnormality. A separate listing of all ALT, AST, total, indirect and direct bilirubin, and alkaline phosphatase values will be provided for each subject who had at least a Grade 3 ALT, AST, alkaline phosphatase, or total bilirubin. A similar listing of all hemoglobin values will be provided for each subject who had at least a Grade 2 hemoglobin value. The listing for hemoglobin will include all hemoglobin, total neutrophils, platelet count and white blood cell count values.

The hemoglobin by maximum CTCAE grade table, described above, also will be provided for subjects with and without treatment-emergent adverse events of dyspnea (defined by PTs of "dyspnoea" or "dyspnoea exertional").

For subjects with a Grade 3 or higher total bilirubin elevation, a listing of treatment-emergent events will be provided that includes all events with PTs in the "Cholestasis and jaundice of hepatic origin" SMQ (broad search) after excluding PTs within the "Investigations" SOC.

Table 12. 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 during the Treatment Period will be calculated:

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

A subject or event will be counted if the post-baseline laboratory values meet the above criteria regardless of the baseline laboratory value (i.e., the post-baseline laboratory value does not need to be worse than the baseline laboratory value). The maximum value will be compared to the ULN to determine if a subject meets the criteria listed above. The maximum values do not have to be concurrent when determining if a subject met the criteria 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.

For subjects meeting the criterion of ALT < 3 × ULN **and** total bilirubin ≥ 2 × ULN, the number and percentage of subjects with a total bilirubin value in the categories of ≤ ULN, > ULN – < 2 × ULN, and ≥ 2 × ULN at the Final Treatment Visit will be calculated. A similar summary will be provided for Post-Treatment Week 4.

In addition, for subjects meeting the criterion of ALT < 3 × ULN **and** total bilirubin ≥ 2 × ULN (based on the maximum value relative to the ULN), the ratio of indirect bilirubin to total bilirubin will be calculated. The following summary statistics will be presented for the ratio at baseline and for the ratio associated with the peak total bilirubin value during the Treatment Period: sample size, mean, standard deviation, minimum, maximum, and median. In addition, the number and percentage of subjects with a ratio < 0.75 and < 0.50 will be presented for baseline and peak.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

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

The Criteria for Potentially Clinically Significant vital sign findings are presented in Table 13.

Table 13. Criteria for Potentially Clinically Significant Vital Sign Values

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

11.4.2 Statistical Methods

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

At each protocol-specified post-baseline visit, including applicable post-treatment visits, vital sign parameters will be summarized with the baseline mean; visit mean; and change from baseline mean, standard deviation, minimum, maximum, and median.

The number and percentage of subjects with post baseline values during the Treatment Period meeting Criteria for Potentially Clinically Significant vital signs values (Table 13) will be calculated. 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 Summary of Changes

12.1 Summary of Changes Between the Latest Version of the Protocol and Version 1 of the SAP

- Added unplanned interim analysis including all subjects to allow for submission to the CFDA at the time of SVR_{12} analysis.
- Deleted planned interim analysis, which was to be conducted after all South Korean and Taiwanese subjects completed the Post-Treatment Week 12 Visit, because the unplanned interim analysis was added.
- Added references for geographic region-specific pegIFN/RBV SVR rates for use in sensitivity analyses of the primary endpoints (Section 4.3) and specified the rates (Section 10.5) to provide details for the sensitivity analyses pre-specified in the protocol.
- Added modified ITT Genotype (mITT-GT) population and modified ITT-Genotype and SVR_{12} Virologic Failure (mITT-GT + VF_{SVR12}) population and modified ITT-Genotype and SVR_{24} Virologic Failure (mITT-GT + VF_{SVR24})

population as populations for sensitivity analyses to exclude SVR failures due to reasons other than virologic failure (Section 5.1 and Section 10.5).

- Added additional summaries of demographics, baseline characteristics, medical history, and previous/concomitant medications by geographic region to provide geographic region-specific information (Section 7.1).
- Provided algorithm for determining a subject's HCV genotype and subtype based on phylogenetic analyses and/or Inno-LiPA 2.0 to guide programming (Section 7.1).
- Changed the unit for IP-10 from pg/mL to ng/L (units are equivalent) to align with the global studies (Section 7.1 and Section 10.7).
- Added summary of hepatoprotective medications taken at baseline to provide additional information on the types of hepatoprotective medications used (Section 7.3).
- Corrected the HCV RNA LLOQ to be 15 IU/mL (Section 10.1).
- Added re-infection definition and further breakdown of Relapse by non-reinfection relapse versus reinfection in Reasons for SVR_{12} non-Response to distinguish between reinfection and true virologic failure due to relapse (Section 10.1).
- Added Modified ITT Genotype (mIA-GT) population and Modified ITT-Genotype and SVR_{12} Virologic Failure (mIA-GT + VF_{SVR12}) population and Modified ITT-Genotype and SVR_{24} Virologic Failure (mIA-GT + VF_{SVR24}) population as populations for sensitivity analyses to exclude SVR failures due to reasons other than virologic failure (Section 10.5).
- Excluded subjects who were categorized as "other" for SVR_{12} (or SVR_{24}) non-response in the alternative imputation methods for sensitivity analyses in order to exclude all subjects without virologic failure (Section 10.5).
- Moved the analysis of the primary endpoints by geographic region from the subgroup analysis section (Section 10.7) to the sensitivity analysis section to align with the Study M13-767 SAP (Section 10.5).
- Added additional sensitivity analysis for SVR_{12} and SVR_{24} in which the LLOQ will be replaced with 25 IU/mL to align with the LLOQ used in the global studies (Section 10.5).

- Added test for homogeneity to align with the global studies (Section 10.5.1).
- Added summaries of secondary efficacy endpoints by geographic region as additional efficacy analyses to provide information by geographic region (Section 10.6).
- Specified that subgroup analyses of SVR_{12} and SVR_{24} would also be performed by geographic region to provide geographic region-specific information (Section 10.7).
- Added a subgroup analysis of SVR_{12} and SVR_{24} for "any of platelets $< 90 \times 10^9$/L, albumin < 35 g/L, or alpha fetoprotein ≥ 20 ng/mL, or none of the three" to provide additional information (Section 10.7).
- Updated the resistance analyses to guide programming (Section 10.8).
- Added eGFR using C-MDRD in Criteria for Potentially Clinically Significant Chemistry Values because this parameter is more applicable to the study's population than calculated creatinine clearance (Section 11.3.1).
- Moved analyses of mean change from baseline in liver function tests (other than Fibrotest) from Additional Efficacy Analyses (Section 10.6) to Analysis of Laboratory Data (Section 11.3) because the parameters are safety parameters.
- Added summaries of hemoglobin and LFTs by CTCAE grade and summaries of ALT and total bilirubin with respect to the ULN to align with the global studies (Section 11.3.2).

13.0 References

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Document Approval

Study M14491 - Statistical Analysis Plan Version 1 - 29Jun2016 (E3 16.1.9)

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Signed by:	Date:	Meaning Of Signature:
[redacted]	29-Jun-2016 06:15:51 PM	Approver
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	30-Jun-2016 05:17:43 PM	Approver

16.1__9.2 CMQ Preferred Terms

The AbbVie drug-induced rash company MedDRA query included the following preferred terms:

Preferred Terms in the AbbVie Drug-Induced Rash Company MedDRA (Version 19.0) Query
Actinic prurigo
Acute generalised exanthematous pustulosis
Administration site abscess sterile
Administration site dryness
Administration site erosion
Administration site exfoliation
Administration site induration
Administration site irritation
Administration site macule
Administration site nodule
Administration site pallor
Administration site papule
Administration site plaque
Administration site pustule
Administration site rash
Administration site scab
Administration site vasculitis
Application site abscess sterile
Application site acne
Application site erythema
Application site hypersensitivity
Application site macule
Application site papules
Application site plaque
Application site pruritus
Application site pustules
Application site rash
Application site urticaria
Application site vasculitis

Preferred Terms in the AbbVie Drug-Induced Rash Company MedDRA (Version 19.0) Query
Application site vesicles
Atopy
Biopsy skin
Biopsy skin abnormal
Bullous impetigo
Butterfly rash
Capillaritis
Catheter site rash
Catheter site urticaria
Chronic pigmented purpura
Conjunctivitis
Corneal exfoliation
Cutaneous lupus erythematosus
Cutaneous symptom
Cutaneous vasculitis
Dermatitis
Dermatitis acneiform
Dermatitis allergic
Dermatitis atopic
Dermatitis bullous
Dermatitis contact
Dermatitis diaper
Dermatitis exfoliative
Dermatitis exfoliative generalised
Dermatitis infected
Dermatitis papillaris capillitii
Dermatitis psoriasiform
Device allergy
Diffuse vasculitis
Drug cross-reactivity
Drug eruption
Drug hypersensitivity
Drug reaction with eosinophilia and systemic symptoms

Preferred Terms in the AbbVie Drug-Induced Rash Company MedDRA (Version 19.0) Query
Dyshidrotic eczema
Eczema
Eosinophilic pustular folliculitis
Eosinophilic pustulosis
Epidermal necrosis
Epidermolysis
Epidermolysis bullosa
Eruptive pseudoangiomatosis
Erythema
Erythema multiforme
Erythrodermic psoriasis
Exfoliative rash
Fixed drug eruption
Generalised erythema
Genital ulceration
Granulomatous rosacea
Haemorrhagic urticaria
Hand dermatitis
Henoch-Schonlein purpura
Henoch-Schonlein purpura nephritis
Hypersensitivity
Hypersensitivity vasculitis
Idiopathic urticaria
Impetigo
Implant site erosion
Implant site exfoliation
Implant site pustules
Implant site rash
Implant site urticaria
Implant site vesicles
Incision site dermatitis
Incision site rash
Incision site ulcer

Preferred Terms in the AbbVie Drug-Induced Rash Company MedDRA (Version 19.0) Query
Incision site vesicles
Infusion site abscess sterile
Infusion site dermatitis
Infusion site discharge
Infusion site discolouration
Infusion site dryness
Infusion site erosion
Infusion site erythema
Infusion site exfoliation
Infusion site hypersensitivity
Infusion site induration
Infusion site inflammation
Infusion site irritation
Infusion site macule
Infusion site nodule
Infusion site pallor
Infusion site papule
Infusion site plaque
Infusion site pruritus
Infusion site pustule
Infusion site rash
Infusion site reaction
Infusion site urticaria
Infusion site vesicles
Infusion site warmth
Injection site dermatitis
Injection site discolouration
Injection site erosion
Injection site erythema
Injection site exfoliation
Injection site hypersensitivity
Injection site induration
Injection site inflammation

Preferred Terms in the AbbVie Drug-Induced Rash Company MedDRA (Version 19.0) Query
Injection site irritation
Injection site macule
Injection site papule
Injection site pruritus
Injection site pustule
Injection site rash
Injection site reaction
Injection site urticaria
Injection site vasculitis
Injection site vesicles
Injection site warmth
Lip exfoliation
Lupus vasculitis
Lupus-like syndrome
Medical device site dermatitis
Medical device site discharge
Medical device site discolouration
Medical device site dryness
Medical device site eczema
Medical device site erosion
Medical device site erythema
Medical device site exfoliation
Medical device site hypersensitivity
Medical device site induration
Medical device site inflammation
Medical device site irritation
Medical device site macule
Medical device site nodule
Medical device site pallor
Medical device site papule
Medical device site plaque
Medical device site pruritus
Medical device site pustule

Preferred Terms in the AbbVie Drug-Induced Rash Company MedDRA (Version 19.0) Query
Medical device site rash
Medical device site scab
Medical device site scar
Medical device site sterile abscess
Medical device site vasculitis
Medical device site vesicles
Microscopic polyangiitis
Mouth ulceration
Mucocutaneous rash
Mucocutaneous ulceration
Mucosal exfoliation
Mucosal necrosis
Mucosal ulceration
Nikolsky's sign
Nodular rash
Ocular vasculitis
Oculomucocutaneous syndrome
Oral mucosal eruption
Oral mucosal exfoliation
Oropharyngeal blistering
Pain of skin
Palmar-plantar erythrodysaesthesia syndrome
Palpable purpura
Papulopustular rosacea
Pemphigoid
Pemphigus
Penile exfoliation
Penile ulceration
Photosensitivity reaction
Polymorphic light eruption
Pruritus
Pruritus allergic
Pruritus generalised

Preferred Terms in the AbbVie Drug-Induced Rash Company MedDRA (Version 19.0) Query
Psoriasis
Purpura
Rash
Rash erythematous
Rash follicular
Rash generalised
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash neonatal
Rash papular
Rash papulosquamous
Rash pruritic
Rash pustular
Rash scarlatiniform
Rash vesicular
Rebound atopic dermatitis
Rebound eczema
Scleroderma-like reaction
Skin exfoliation
Skin irritation
Skin necrosis
Skin reaction
Skin toxicity
Stevens-Johnson syndrome
Stoma site extravasation
Stomatitis
Systemic lupus erythematosus rash
Tongue eruption
Tongue exfoliation
Toxic epidermal necrolysis
Toxic skin eruption

Preferred Terms in the AbbVie Drug-Induced Rash Company MedDRA (Version 19.0) Query
Transient neonatal pustular melanosis
Type I hypersensitivity
Type II hypersensitivity
Type III immune complex mediated reaction
Type IV hypersensitivity reaction
Urticaria
Urticaria contact
Urticaria vesiculosa
Urticarial vasculitis
Vaccination site dermatitis
Vaccination site discolouration
Vaccination site eczema
Vaccination site erosion
Vaccination site erythema
Vaccination site exfoliation
Vaccination site extravasation
Vaccination site hypersensitivity
Vaccination site hypertrichosis
Vaccination site induration
Vaccination site inflammation
Vaccination site irritation
Vaccination site macule
Vaccination site pallor
Vaccination site papule
Vaccination site plaque
Vaccination site pruritus
Vaccination site rash
Vaccination site reaction
Vaccination site urticaria
Vaccination site vasculitis
Vaccination site vesicles
Vaccination site warmth
Vaginal exfoliation

Preferred Terms in the AbbVie Drug-Induced Rash Company MedDRA (Version 19.0) Query
Vaginal ulceration
Vasculitic rash
Vulval ulceration
Vulvovaginal rash