1.0 Title Page

Statistical Analysis Plan

Study M13-101

An Open-Label Study to Evaluate the Safety, Antiviral Activity, and Pharmacokinetics of Direct-Acting Antiviral Agent (DAA) Treatment in Combination with Peginterferon α-2a and Ribavirin (pegIFN/RBV) in Chronic Hepatitis C Virus (HCV) Infected Subjects Who Have Experienced Virologic Failure in a Previous AbbVie or Abbott DAA Combination Study

Date: 05 May 2017

Version 1.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed by AbbVie Statistics and Statistical Programming for study Protocol M13-101 dated 26 June 2015 and incorporates 10 amendments and 5 administrative changes. The SAP provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work.

This is the first version of the SAP for Protocol M13-101. Unless noted otherwise, all analyses will be performed using SAS version 9.3 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

4.1.1 Primary Objective

The primary objective of this study is to evaluate the safety and antiviral efficacy, defined as the percentage of subjects with sustained virologic response 12 weeks post-dosing (SVR_{12}; HCV RNA < LLOQ 12 weeks after the last dose of study drug), of the study regimen.

4.1.2 Secondary Objective

The secondary objectives of this study are:

- to evaluate the percentage of subjects with sustained virologic response 24 weeks post-dosing (SVR_{24}; HCV RNA < LLOQ 24 weeks after the last dose of study drug) and
- to evaluate the percentage of subjects with extended rapid virologic response (eRVR) (HCV RNA < LLOQ at Weeks 4 through 12 of therapy with ABT-450/r plus ABT-267 plus pegIFN plus RBV).

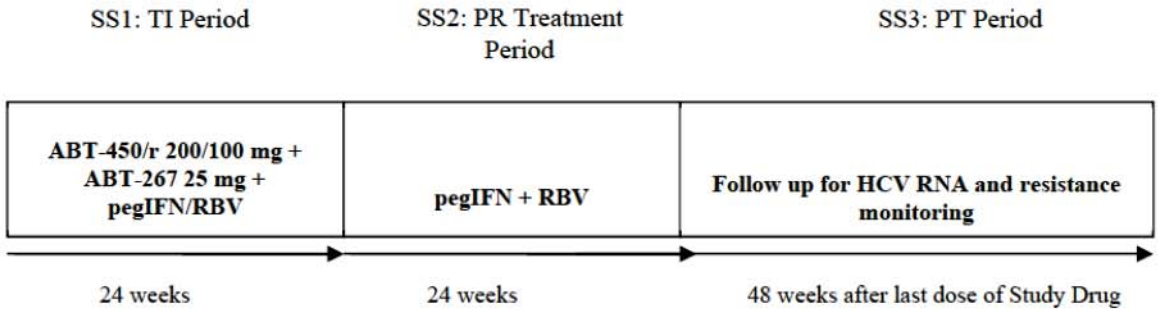
4.2 Design Diagram

This is a multicenter, Phase 2, open-label, single-arm, combination treatment study evaluating ABT-450/r in combination with ABT-267, pegIFN and RBV for 24 weeks followed by pegIFN and RBV alone for an additional 24 weeks in HCV genotype 1-infected subjects who have experienced virologic failure while participating in a previous pegIFN-free Abbott/AbbVie DAA combination study. This study consists of a pre-screening period, a screening period and three substudies:

- Substudy 1 (Treatment Intensification [TI]): 24 weeks of therapy with ABT-450/r plus ABT-267 plus pegIFN plus RBV;
- Substudy 2 (pegIFN/RBV [PR] Treatment): 24 weeks of pegIFN and RBV therapy alone;
- Substudy 3 (Post-treatment [PT] Follow-up Period): 48 weeks after last dose of any study drug for resistance monitoring and HCV RNA viral load testing.

A study schematic is shown below (Figure 1).

Figure 1. Study M13-101 Schematic



There is one treatment group for this study. During Substudy 1 (TI Period), subjects will receive ABT-450/r 200/100 mg daily (QD), ABT-267 25 mg QD, pegIFN 180 µg once weekly, and weight-based RBV twice daily. During Substudy 2 (PR Treatment

Period), subjects will receive 24 weeks of pegIFN/RBV. All subjects who receive at least one dose study drug will be followed for 48 weeks in the Post-Treatment period. The duration of the study will be 96 weeks, not including a screening period.

4.3 Sample Size

There is no predetermined sample size for this study. Subjects who experience virologic failure in previous Abbott/AbbVie DAA combination studies and who meet the eligibility criteria will be treated in this study.

4.4 Interim Analysis

There will be no interim analysis. Final analysis will occur after all enrolled subjects have completed the Post-Treatment Period or prematurely discontinued from the study. Data will be locked after performing appropriate data cleaning.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population will consist of all enrolled subjects who receive at least one dose of study drug. Efficacy analyses will be performed on the ITT population.

Modified Intent-to-Treat (mITT) Population

A sensitivity analysis of SVR_{12} as described in Section 10.4, when applicable, will be performed on the intent-to-treat population modified to exclude subjects who are not of HCV genotype 1 infection and the subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-VF).

Safety Population

Subjects who receive at least one dose of study drug will be included in the safety population. The safety population will be the same as the ITT population for this study.

Safety, demographic, and baseline characteristics will be analyzed for the safety population. No imputations for missing data will be performed for analyses of safety data.

5.2 Variables Used for Stratification of Randomization

There is no randomization for this study.

6.0 Analysis Conventions

The final analyses will be conducted by statisticians and statistical programmers at AbbVie according to the methodologies specified in this SAP. Any deviations from the planned statistical analysis will be described and justified in the final clinical study report, as appropriate.

6.1 Definition of Baseline and Final Assessment

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 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.

If multiple measurements are recorded on the same day, the last measurement recorded prior to dosing will be used as Baseline. 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 TI, PR, and PT Periods.

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

Study days are calculated for each time point relative to the first dose of study drug. They are defined as the number of days between the day of the first dose of study drug and the

specific time point. 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. The day of the first dose of study drug is defined as Study Day 1, while the day prior to the first study drug dose is defined as Study Day –1 (i.e., there is no Study Day 0).

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

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

Definition of Final DAA Treatment Visit Value

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

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

Study drug end Days are calculated relative to the last pegIFN injection + 7 days. The last day of pegIFN injection + 7 days 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 Visit Value

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

Final Post-Treatment Value

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

6.2 Definition of Analysis Windows

The time windows specified in Table 1 for Substudy 1, Table 2 for Substudy 2 and Table 3 for Substudy 3 describe how data are assigned to protocol specified time points. Time windows specified in Tables 1 and 2 will also be used for resistance analyses. However, for resistance analyses, the windows relative to the end of DAA dosing (Table 2) will be irrespective of the end of pegIFN/RBV dosing.

The subject will continue to be monitored for antiviral drug resistance for 48 weeks following the last dose of study drug. If the subject discontinues DAA study drug/Substudy 1 and continues to receive pegIFN/RBV, the subject will follow the PR Treatment visit schedule, as specified in Table 2, and then subsequently follow the Post-Treatment visit schedule, as specified in Table 3, following the last dose of pegIFN/RBV. However, if the subject discontinues DAA study drug and pegIFN/RBV, the subject will follow the Post-Treatment visit schedule for 48 weeks following the last dose of study drug, specified in Table 3.

If more than one assessment is included in a time window, the assessment closest to the nominal time should be used. If there were two observations equal distant to the nominal time the latest one will be used in analyses. The only exception to this is for the SVR windows; for these windows, the last value in the window will be used.

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

Table 1. DAA + PR Treatment (TI Period, Substudy 1) Visit Windows

Scheduled Time	Nominal Day (Study Day)	Time Window (Study Days Range)
Baseline	1	≤ 1
TI Week 1	7	2 to 10
TI Week 2	14	11 to 21
TI Week 4	28	22 to 42
TI Week 8	56	43 to 70
TI Week 12	84	71 to 98
TI Week 16	112	99 to 126
TI Week 20	140	127 to 154
TI Week 24	168	155 to 182
Final DAA Treatment Visit	Last Visit with Study Day > 1 and DAA Study Drug End Day ≤ 2	

Notes: Data must also have DAA study drug end day ≤ 2 for all windows.
The result closest to the scheduled time point will be used.

Table 2. PR Treatment (Substudy 2)/Post-DAA Visit Windows

Scheduled Time	Nominal Study (DAA Study Drug End Day)	Time Window (DAA Study Drug End Days Range)
PR/Post-DAA Week 2	14	3 to 21
PR/Post-DAA Week 4	28	22 to 42
PR/Post-DAA Week 8	56	43 to 70
PR/Post-DAA Week 12	84	71 to 126
PR/Post-DAA Week 24	168	127 to 210
PR/Post-DAA Week 36[a]	252	211 to 294
PR/Post-DAA Week 48[a]	336	295 to 378
Final Treatment Visit[b]	Last Visit with Study Day > 1 and Study Drug End Day ≤ 2	

a. These Substudy 2 visits are only needed for subjects who did not complete 24 weeks for pegIFN/RBV in Substudy 1 such that a subject completes a total of 48 weeks of pegIFN/RBV across Substudies 1 and 2. However, the Post-DAA Week 48 window may be used for resistance analyses, regardless of the number of Substudy 2 visits.

b. Final Treatment Visit is defined for all subjects, regardless of whether the subject enters Substudy 2.

Note: For efficacy analyses of HCV RNA and safety analyses, all scheduled time points, except Final Treatment Visit, will apply only to subjects who received pegIFN/RBV in Substudy 2.

For efficacy analyses of HCV RNA and safety analyses, data must also have DAA Study Drug End Day > 2 and PR End Day ≤ 2 for all scheduled time points, except Final Treatment Visit.

For resistance analyses, data must have DAA Study Drug End Day > 2 for all scheduled time points. Resistance data included in Post-DAA windows may have been collected either during PR Treatment or Post-Treatment.

The result closest to the scheduled timepoint will be used.

Table 3. Post-Treatment (Substudy 3) Visit Windows

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

Notes: The result closest to the scheduled timepoint will be used, except for SVR endpoints. For SVR windows, the last value in the window will be used.

Blood samples for chemistry, hematology, and urinalysis are only scheduled to be collected at PT Weeks 2 and 4 during the Post-Treatment Period.

HCV RNA measurements taken after the start of another anti-viral treatment will be excluded.

6.3 Definition of Missing Data Imputation

Imputations for missing data will be performed when analyzing RVR, Final Treatment Visit Response, eRVR, and all SVR endpoints.

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 flanking imputation, regardless of the value chosen for the subsequent and preceding window.

For 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 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.

For analyses of RVR, Final Treatment Visit Response, eRVR, and SVR, subjects still missing a value for the visit window associated with the analysis after performing the imputations described above will be imputed as a failure.

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.

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

7.1 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Safety Population.

Demographics include age, weight, and body mass index (BMI) as continuous variables, and gender, race ethnicity, age category (< 50 years and ≥ 50 years; < 65 years and ≥ 65 years), birth year (< 1945, 1945 to 1965, > 1965), BMI category (< 30 kg/m^2 and ≥ 30 kg/m^2), and geographic region (North America, Europe, Australia/New Zealand, Latin America), original study as categorical variables. Baseline characteristics will include HCV genotype/subtype (1a, 1b, other 1 subtype), IL 28B genotype (CC, CT, and TT; CC and non-CC), initial DAA combination study prior to Study M13-101, treatment

status at entry to initial DAA combination study prior to Study M13-101 (treatment naïve or treatment experienced [null responder, partial responder or relapser]), type of response to HCV treatment in initial DAA combination study (null responder, partial responder, relapser), treatment in the initial DAA combination study, baseline $\log_{10}$ HCV RNA levels (continuous), history of diabetes, baseline fibrosis score (F0 – F1, F2, F3, F4), baseline HCV RNA levels (< 800,000 IU/mL or ≥ 800,000 IU/mL), baseline IP-10 (< 600 ng/L or ≥ 600 ng/L) and baseline HOMA-IR (fasting glucose [MMOL/L] × fasting insulin [MCIU/ML]/22.5, < 3 mU × mmol/L^2 or ≥ 3 mU × mmol/L^2). Subjects who do not have a fasting glucose and fasting insulin value at Baseline will be excluded from the summary of baseline HOMA-IR.

Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI). The number and percentage of subjects will be presented for categorical variables (e.g., gender and race). Summary statistics for baseline weight will be computed overall and separately by gender.

IL28B rs12979860 genotype was resulted as C/C, C/T, T/T, or Unable to Assign Genotype by the central laboratory or Abbott/AbbVie Pharmacogenetics group in the initial DAA combination study.

History of diabetes is defined as presence of "Metabolic/Diabetes mellitus" on the MH eCRF.

Baseline fibrosis stage is defined for subjects with non-missing liver biopsy scores, FibroScan scores, or FibroTest scores in the initial DAA combination study. In general, subjects will be categorized as F0 – F1, F2, F3, or F4 according to the Metavir mapping defined in Table 4. If a subject has more than one score recorded, then only one score will be used to categorize the subject. If a biopsy score is present, then it will be used to categorize the subject, regardless of the FibroScan/FibroTest score. Similarly, if a FibroScan score is present along with a FibroTest score, then the FibroScan score will be used to categorize the subject. If biopsy and FibroScan scores are not present and more than one FibroTest result is available, then the Baseline FibroTest result (i.e., last

non-missing FibroTest result on or before Day 1 of the initial DAA combination study) will be used to categorize the subject. In some studies, the investigator used the mapping and put the result in the eCRF and this result is used directly per the initial DAA combination study SAP.

Table 4. Baseline Fibrosis Stage

Baseline Fibrosis Stage, Metavir Equivalents	Liver Biopsy Metavir, Batts Ludwig, Knodell, IASL, Scheuer, New Inuyama or Laennec Score	Liver Biopsy Ishak Score	FibroScan (kPa)	FibroTest
F0 – F1	0 or 1	0, 1, or 2	< 8.8	≤ 0.48
F2	2	3	≥ 8.8 to < 9.6	0.49 to 0.58
F3	3	4	≥ 9.6 to < 14.6	≥ 0.59 to 0.72
F4	4	≥ 5	≥ 14.6	≥ 0.73

7.2 Medical History

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

The subject's medical history will be transferred from the initial Abbott/AbbVie DAA combination study to the Study M13-101 EDC system. The subject's medical history will then be updated at the Screening Visit with any relevant information that was not collected in the initial Abbott/AbbVie DAA combination study and any new medical history that occurred between the end of the initial Abbott/AbbVie DAA combination study and this study. The subject's medical history will also be updated if needed for the

period between the Screening Visit and the TI Day 1 Visit. The updated medical history as of TI Day 1 will serve as the baseline for clinical assessment.

7.3 Previous HCV Treatment and Concomitant Medications

Prior HCV medications, concomitant medications and post-DAA treatment HCV medications will be summarized for the Safety Population. A prior HCV medication is defined as pegIFN/RBV after terminating the initial Abbott/AbbVie DAA combination study and prior to enrolling in Study M13-101 and also the study drug regimen taken in the initial Abbott/AbbVie combination DAA trial. A concomitant medication is defined as any medication that started prior to the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started after the first dose of study drug, but not after the last dose of DAA study drug. Medications related to HCV antiviral therapy and medications prescribed in association with treatment due to an SAE will be collected during Substudy 2 and Substudy 3. Post-DAA treatment medications related to HCV antiviral therapy will be summarized and are defined as any medications started on or after the last dose of DAA study drug and entered as a post-treatment HCV medication on the eCRF.

The number and percentage of subjects taking concomitant medications and post-treatment HCV medications will be summarized based on the WHO Drug Dictionary.

8.0 Patient Disposition

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

- Enrolled subjects
- Subjects who took at least one dose of DAA study drug in Substudy 1
- Subjects who discontinued DAA treatment in Substudy 1
- Subjects who completed DAA treatment
- Subjects who continued into Substudy 2

- Subjects who discontinued pegIFN/RBV (i.e., subjects who did not enter Substudy 2 or subjects who entered Substudy 2 and prematurely discontinued pegIFN/RBV during Substudy 2)
- Subjects who completed the study
- Subjects who discontinued from the study

The number and percentage of subjects who discontinued study drug in Substudies 1 and 2 will be summarized by reason (all reasons) and by primary reason (collected on eCRF). The number and percentage of subjects who discontinued from the study will be summarized by reason (all reasons) and by primary reason as recorded on the eCRF.

The number and percentage of subjects RBV dose modification will be summarized. Reasons for study drug interruptions and RBV dose modifications will be presented in the listings.

9.0 Study Drug Exposure and Compliance

The duration of exposure to DAA therapy will be summarized overall for the Safety Population. Duration of exposure is defined for each subject as the last DAA dose date minus the first DAA dose date plus 1 day (i.e., any study drug interruptions will not be subtracted out). Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented. The duration of DAA therapy will also be summarized with frequencies and percentages using the following categories: 1 to 30 days, 31 to 60 days, 61 to 90 days, 91 to 120 days, 121 to 150, and $\geq$ 151 days.

Similarly, the duration of exposure to pegIFN and RBV across Substudies 1 and 2 will be summarized. Duration of exposure to pegIFN therapy across Substudies 1 and 2 is defined for each subject as the last pegIFN injection date minus first pegIFN injection date plus 7 days and will be summarized and analyzed similarly to DAA. Duration of exposure to RBV therapy across Substudies 1 and 2 is defined for each subject as the last RBV dose date minus first RBV dose date plus 1 day and will be summarized and analyzed similarly to DAA. The following categories will be used for pegIFN and RBV:

1 to 30 days, 31 to 60 days, 61 to 90 days, 91 to 120 days, 121 to 150 days, 151 to 180 days, 181 to 210 days, 211 to 240 days, 241 to 270 days, 271 to 300 days, 301 to 330 and ≥ 331 days.

The compliance to each DAA study drug (ABT-450, ABT-267) and ritonavir during the first 24 weeks of treatment (Substudy 1) will be calculated as the percentage of capsules/tablets taken over the total capsules/tablets prescribed. The total number of capsules/tablets prescribed will be equal to the total number of capsules/tablets that should have been taken per the protocol for the duration that the subject was in the TI Period (Substudy 1). Study drug interruptions captured on the eCRF will be subtracted when calculating compliance. Compliance will be summarized with the mean, median, standard deviation, minimum and maximum percentage for each DAA and ritonavir. A subject is considered to be compliant if the percentage is between 80% and 120% during the first 24 weeks of treatment (Substudy 1). The percentage of subjects who are compliant to each study drug will be summarized. A subject listing of compliance will be provided also.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

All efficacy analyses will be performed for the ITT population, unless otherwise specified. Analyses of primary and secondary endpoints will be performed for the overall treatment cohort. No statistical comparisons will be made. Analyses of additional endpoints will be performed for the overall treatment cohort. A 95% confidence interval based on Wilson score test will be provided.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay V2.0. For this assay, the LLOD is 15 IU/mL and the LLOQ is 25 IU/mL. HCV RNA results that are detectable but not quantifiable are reported as

"< 25 IU/mL HCV RNA detected" and those that are undetectable are reported as "HCV RNA not detected" in the database.

The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 25 IU/mL, including values reported as "HCV RNA NOT DETECTED" or "< 25 IU/mL HCV RNA DETECTED." HCV RNA ≥ LLOQ are all quantifiable values of 25 IU/mL or greater.

If a subject discontinues the study drug and subsequently starts another HCV treatment, this subject's HCV RNA values after the time he/she starts another HCV treatment will be excluded from analyses.

All HCV RNA endpoints will be defined using the LLOQ. Imputations for missing values will be performed for analyses of RVR, Final Treatment Visit response, eRVR, SVR_4, SVR_{12}, SVR_{24} as specified in Section 6.0.

Definitions for Efficacy Endpoints

Note that a confirmed quantifiable post-treatment value is defined as any 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.

RVR (Rapid Virologic Response) = HCV RNA < LLOQ at TI Week 4.

eRVR (extended rapid virologic response) = HCV RNA < LLOQ at TI Weeks 4 through 12 without a confirmed HCV RNA ≥ LLOQ between TI Weeks 4 and 12.

Final Treatment Visit Response = HCV RNA < LLOQ at the end of treatment (i.e., at completion of all study drugs: DAAs, pegIFN, and RBV); this corresponds to the Final Treatment Visit value (see Section 6.0).

Breakthrough = 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 breakthrough value (≥ LLOQ or > 1 $\log_{10}$ above nadir) followed by lost to follow-up would be considered a breakthrough (i.e., will not require confirmation).

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

SVR_{24} (referred to as $SVR_{24actual}$ in the protocol) = HCV RNA < LLOQ in the SVR_{24} window (24 weeks after the last actual dose of study drug [including DAA, pegIFN, and RBV]) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

SVR_{12} (referred to as $SVR_{12actual}$ in the protocol) = HCV RNA < LLOQ in the SVR_{12} window (12 weeks after the last actual dose of study drug [including DAA, pegIFN, and RBV]) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

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

$Relapse_{12}$ = confirmed HCV RNA ≥ LLOQ between Final Treatment Visit and 12 weeks after last actual dose of study drug (up to and including SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at the Final Treatment Visit who completes treatment. Completion of treatment is defined as DAA duration ≥ 161 days and pegIFN/RBV duration ≥ 252 days.

$Relapse_{24}$ = 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.

Relapse$_{overall}$ = confirmed HCV RNA ≥ LLOQ between Final Treatment Visit 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. Completion of treatment is defined as DAA duration ≥ 161 days and pegIFN/RBV duration ≥ 252 days.

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.

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.

Reasons for SVR_{12} Non-response

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

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. Relapse (defined according to the **Relapse$_{12}$** definition for subjects who complete treatment);
3. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{12} non-responder who prematurely discontinued study drug 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

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

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. $Relapse_{12}$;
3. $Relapse_{24}$;
4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{24} non-responder who prematurely discontinued study drug and did not meet the On-treatment virologic failure definition);
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 $SVR_{24\ non\text{-}responder}$ not meeting the definitions of (1) – (5), such as a subject with a single quantifiable value within the SVR_{24} window followed by an undetectable value beyond the SVR_{24} window).

10.2 Primary Efficacy Analysis

The primary efficacy endpoint is the percentage of subjects with sustained virologic response 12 weeks after the last actual dose of study drug (including DAA, pegIFN, and RBV) (SVR_{12}; HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The percentage of subjects with SVR_{12} and the corresponding 95% Wilson score confidence interval will be calculated.

10.3 Secondary Efficacy Analyses

The secondary efficacy endpoints are the percentage of subjects with sustained virologic response 24 weeks after the last actual dose of study drug (including DAA, pegIFN, and RBV) (SVR_{24}; HCV RNA < LLOQ 24 weeks after the last actual dose of study drug) and the percentage of subjects with eRVR (HCV RNA < LLOQ at TI Weeks 4 through 12).

The percentage of subjects with SVR_{24} and eRVR and the corresponding 95% Wilson score confidence intervals will be calculated.

A subject will be considered to have e RVR if after all missing data are imputed according to rules specified in Section 6.0, he/she has HCV RNA levels below LLOQ at TI Week 4 and TI Week 12 with no confirmed HCV RNA ≥ LLOQ in between. If a subject is missing HCV RNA data at either TI Week 4 or 12 then the subject will be considered an eRVR failure.

10.4 Sensitivity Analyses for SVR

A sensitivity analysis of SVR_{12} will be conducted using a Modified Intent-to-Treat Genotype and Virologic Failure (mITT-GT -VF) population. The number and percentage of subjects in the mITT-GT-VF population achieving SVR_{12} and the corresponding 95% Wilson score confidence interval will be calculated.

10.5 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized for the overall treatment group as specified:

- the percentage of subjects with unquantifiable HCV RNA at each post-baseline visit throughout the Substudy 1 using data from the central laboratory as observed (i.e., no imputation for missing data);
- the percentage of subjects with RVR (per RVR definition);
- the percentage of subjects with Final Treatment Visit response (per Final Treatment Visit response definition);
- the percentage of subjects achieving SVR_4;
- the percentage of subjects with on-treatment virologic failure (per on-treatment virologic failure definition);
- the percentage of subjects who experienced $Relapse_{12}$ (per $Relapse_{12}$ definition);

- the percentage of subjects who experienced $Relapse_{24}$ (per $Relapse_{24}$ definition);
- the percentage of subjects who achieved SVR_{24} who subsequently relapsed ($Relapse_{late}$);
- the percentage of subjects who experienced $Relapse_{overall}$ (per $Relapse_{overall}$ definition).

The percentage of subjects with RVR, Final Treatment Visit Response, SVR, on-treatment virologic failure and post-treatment relapse will be calculated with two-sided 95% confidence intervals using the Wilson score method. Imputation methods, as described in Section 6.0, will be used when summarizing each of these endpoints.

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

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_{12} and SVR_{24} out of all subjects who achieved SVR_{12}. The NPV of SVR_{12} on SVR_{24} is the proportion of subjects who do not achieve SVR_{12} and SVR_{24} out of all subjects who did not achieve SVR_{12}.

The number and percentage of subjects who fail to suppress HCV RNA and received at least 6 weeks of treatment (study drug duration $\geq$ 36 days) will be tabulated per treatment arm along with the subject numbers corresponding to the subjects who failed to suppress.

The number of subjects who breakthrough at any time during treatment and within each protocol-specified visit (defined in Table 1 and Table 2) will be summarized along with a corresponding listing displaying the subject numbers at the first occurrence of breakthrough.

The number of completers (defined as DAA duration ≥ 161 days and pegIFN/RBV duration ≥ 252 days) who relapse within the SVR_4 window, within the SVR_{12} window, within the SVR_{24} window (defined in Table 3), outside of the SVR_{24} window (PR end day > 210), and anytime post-treatment, $Relapse_{overall}$, (study drug end day ≥ 2) will be summarized along with a corresponding listing displaying the first occurrence of relapse. A similar table and listing will be provided of Preterm Relapses for subjects who prematurely discontinued study drug (defined as DAA duration < 161 days and/or pegIFN/RBV duration < 252 days).

10.6 Resistance Analyses

The genes of interest for population sequencing in this study are those encoding full length NS3/4A and NS5A, while for clonal sequencing they are those encoding NS3 amino acids 1 to 181 and NS5A amino acids 1 to 215. For each DAA target, signature amino acid positions are 1) for paritaprevir: 36, 43, 55, 56, 80, 155, 156, and 168 in NS3 for genotype 1a; 55, 56, 155, 156, and 168 in NS3 for genotype 1b; and 2) for ombitasvir: 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93 in NS5A for genotype 1a; 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93 in NS5A for genotype 1b. The prototypic reference sequences used for analysis will be H77 for genotype 1a or Con1 for genotype 1b. Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of virologic failure is < 1000 IU/mL, the sample closest in time after the failure with an HCV RNA level ≥ 1000 IU/mL will be used. Clonal sequencing of a given target will be performed only if no variants are detected at signature amino acid positions by population sequencing in that sample. In addition, clonal sequencing may be performed if there is a complex mixture of amino acids at one or more signature position that cannot be resolved by population sequencing.

Included time points for analyses on samples from subjects who experience virologic failure (as defined in Section 5.4.1.1) are (1) time of virologic failure or sample closest in time after failure with an HCV RNA level of ≥ 1000 IU/mL, (2) 24 weeks post-DAA treatment, provided that variants at signature amino acid positions were detected by either population or clonal sequencing at the time of failure, and (3) 48 weeks post-DAA treatment, provided that variants at signature amino acid positions were detected by either population or clonal sequencing at post-DAA treatment Week 24.

The following definitions will be used in the resistance analyses:

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

For those subjects whose baseline sample has an HCV RNA level ≥ 1000 IU/mL, a listing by subject of all baseline variants relative to prototypic reference sequence at signature amino acid positions will be provided for each DAA target (NS3 andNS5A).

The following analyses will be performed on the samples from subjects who experienced virologic failure and have post-baseline resistance data available.

The HCV amino acid sequence as determined by population sequencing will be compared with the baseline and appropriate prototypic reference amino acid sequences. Listings by subject of all post-baseline variants detected by population sequencing relative to the baseline amino acid sequences will be provided for each DAA target (NS3 and NS5A). In addition, listings by subject of variants detected by population sequencing at signature amino acid positions relative to baseline and the appropriate prototypic reference amino acid sequences will be provided.

For the subset of samples for which clonal sequencing is performed, the amino acid variants determined by clonal sequencing will be summarized by counting the number of clones whose amino acid sequence does not match that of the prototypic reference sequence by subject at each time point and amino acid position, out of the total number of clones analyzed. Listings by subject of post-baseline variants at signature positions detected by clonal sequencing will be provided for each DAA target.

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

10.7 Handling of Multiplicity

There will be no adjustment for multiple endpoints.

10.8 Efficacy Subgroup Analysis

To evaluate the impact of various baseline characteristics on treatment effect, analyses will be performed for the primary efficacy variable of SVR_{12} using the following subgroups.

- HCV subtype (1a, 1b, or other)
- IL28B genotype (CC or non-CC)

- Race (black or non-black)
- Gender (male or female)
- Age < 65 yrs or ≥ 65 yrs)
- BMI (< 30 kg/m^2 or ≥ 30 kg/m^2)
- Type of response to HCV treatment in initial DAA combination study (treatment-naïve or treatment-experienced [null responder, partial responder, relapser])
- Baseline HCV RNA levels (< 800,000 or ≥ 800,000)
- Subjects with RBV dose modifications (yes or no)
- History of diabetes (yes or no)
- Baseline fibrosis score (F0 – F1, F2, F3 or F4)
- Achievement of eRVR (yes, no)
- Treatment in the initial DAA combination study

The number and percentage of subjects achieving SVR_{12} within each subgroup will be provided for all subgroups. If there are 2 or more subjects within the subgroup level, then two-sided 95% confidence intervals will be calculated using the Wilson score method.

11.0 Safety Analysis

11.1 General Considerations

All subjects who receive at least one dose of study drug will be included in the safety analyses. Safety data will be summarized only for the overall treatment cohort and not by prior treatment.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events

Unless otherwise specified, summaries of adverse events will include adverse events that are treatment-emergent relative to dosing of the DAAs. Treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of study

drug through 30 days after the last dose of DAA 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).

Adverse event data will be summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the clinical study report. The system organ classes will be presented in alphabetical order and the PT will be presented in alphabetical order within each SOC.

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 each of the following adverse event categories:

- Treatment-emergent adverse events
- Treatment-emergent adverse events possibly or probably related to DAAs
- Treatment-emergent adverse events possibly or probably related to pegIFN
- Treatment-emergent adverse events possibly or probably related to RBV
- Treatment-emergent severe adverse events
- Treatment-emergent serious adverse events
- Treatment-emergent adverse events leading to study drug (all study drugs) discontinuation
- Treatment-emergent adverse events leading to interruption of study drug (all study drugs)
- Treatment-emergent adverse events leading to RBV dose modifications
- Treatment-emergent adverse events leading to pegIFN dose modifications
- Treatment-emergent adverse events leading to death

- Deaths

Adverse Event by SOC and PT

For each of the following events, the number and percentage of subjects experiencing treatment-emergent events will be tabulated by SOC and preferred term (PT):

- Treatment-emergent adverse events
- Treatment-emergent adverse events possibly or probably related to DAAs
- Treatment-emergent adverse events possibly or probably related to pegIFN
- Treatment-emergent adverse events possibly or probably related to RBV
- Severe treatment-emergent adverse events

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

Adverse Events by PT

The number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to preferred term and sorted by overall frequency. A similar summary will be provided for treatment-emergent adverse events possibly or probably related to DAAs.

Adverse Event of Special Interest

Specific treatment-emergent adverse events of special interest, which may be searched using Standardized, Company or Product MedDRA Queries (SMQs, CMQs, or PMQs), will be summarized. The search criteria for the adverse events of interest are as follows:

- Severe Cutaneous Reactions using the SMQ "Severe cutaneous adverse reactions" (narrow search)

- Hepatic Decompensation and Hepatic Failure (cases identified by the PMQ)
- Hepatocellular carcinoma identified by the following MedDRA preferred terms: hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, and hepatic cancer metastatic

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

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

Adverse Events by Maximum Severity

Treatment-emergent adverse events will also be summarized by maximum severity of each preferred term. A similar summary will be provided for treatment-emergent adverse events possibly or probably related to DAAs. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity, "Severe." In this case, the subject will be counted under the "Severe" category.

Adverse Events by Maximum Severity Grade Level

Treatment-emergent adverse events will be summarized by maximum severity grade level of each preferred term. Each preferred term will be assigned 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. Non-serious 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 non-serious adverse event with unknown severity, then the subject will be counted in the severity grade level category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another

occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Grade 3" category. Similarly, if a subject has an adverse event with unknown seriousness, then the subject will be counted in the severity grade level category of "unknown" unless the subject has another occurrence of the same adverse event that is marked serious. In this case, the subject will be counted under the "Grade 4" category.

Adverse Events by Maximum Relationship

Treatment-emergent adverse events will also be summarized by maximum relationship of each preferred term to DAA study drug, pegIFN, and RBV, as assessed by the Investigator. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Probably Related" or "Possibly Related." In this case, the subject will be counted under the "Probably Related" or "Possibly Related" category, respectively.

11.2.2 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

The number and percent of subjects experiencing treatment-emergent SAEs (including deaths), treatment-emergent adverse events leading to discontinuation of study drug (all study drugs), treatment-emergent adverse events leading to interruption of study drug (all study drugs), treatment-emergent adverse events leading to RBV dose modifications, treatment-emergent adverse events leading to pegIFN dose modifications, and treatment-emergent adverse events leading to death will be tabulated according to the primary SOC and PT.

In addition, the number and percentage of subjects with adverse events leading to RBV dose modifications and adverse events leading to pegIFN dose modifications will be tabulated according to the primary SOC and PT, using adverse events with an onset date greater than 30 days post-DAA dosing through 30 days after the last dose of

pegIFN/RBV. For these summaries, only subjects with the maximum of (last RBV dose date, last pegIFN dose date + 7) greater than DAA Study Drug End Day 1 (e.g., last DAA dose date + 1) will be included.

11.2.3 Listings of Adverse Events

The following listings will be provided.

- Listing of subject numbers associated with treatment-emergent adverse events grouped by the primary MedDRA SOC and PT.
- Listing of all treatment-emergent serious adverse events.
- Listing of all treatment-emergent adverse events leading to death.
- Listing of treatment-emergent adverse events leading to discontinuation of study drug (all study drugs).
- Listing of treatment-emergent adverse events leading to interruption of study drug (all study drugs).
- Listing of treatment-emergent adverse events leading to RBV dose modifications.
- Listing of treatment-emergent adverse events leading to pegIFN dose modifications.
- Listing of All Serious Adverse Events (from the Time the Subject Signed the Study Specific Informed Consent Through the End of the Study).

11.3 Analysis of Laboratory Data

Data collected from the local laboratory as a result of additional testing due to an SAE will be used in analyses in addition to the data collected from the central laboratory.

11.3.1 Variables and Criteria Defining Abnormality

Hematology variables include: hematocrit, hemoglobin, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, platelet count, neutrophils, bands (if detected), lymphocytes, monocytes, basophils (if detected), eosinophils (if detected),

absolute neutrophil count (ANC), prothrombin time, international normalized ratio, and activated partial thromboplastin time (aPTT).

Chemistry variables include: albumin, serum glutamic pyruvic transaminase, (SGPT/ALT), serum glutamic oxaloacetic transaminase (SGOT/AST), alkaline phosphatase, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, cholesterol (total), creatinine, calculated creatinine clearance (using Ccroft Gault equation), direct and indirect bilirubin, gamma glutamyl transferase (GGT), glucose, inorganic phosphorus, magnesium, potassium, sodium, total bilirubin, total protein, triglycerides, TSH, free T4 (if measured) and uric acid.

Urinalysis variables include: specific gravity, ketones, pH, protein, blood, glucose, urobilinogen, bilirubin, leukocyte esterase, and microscopic (reflex).

Additional variables include: IP-10 and total insulin. IP-10 is measured at TI Day 1, TI Week 4, TI Week 24/TI D/C, PR Final/PR D/C, PT Week 24, and PT Week 48/PT D/C. Total insulin is measured at TI Day 1.

The criteria for Potentially Clinically Significant Laboratory Findings are described in Table 5 and Table 6.

Table 5. Criteria for Potentially Clinically Significant Hematology Values

Test/Units	Very Low (VL)	Very High (VH)
Hemoglobin		
(mmol/L)	< 4.9	
(g/dL)	< 8.0	
(g/L)	< 80	
Platelet Count		
(cells/mm^3)	< 50,000	
(cells/L)	$< 50 \times 10^9$	
WBC Count		
(cells/mm^3)	< 2,000	> 20,000
(cells/L)	$< 2.0 \times 10^9$	$> 20 \times 10^9$
ANC		
(cells/mm^3)	< 1,000	
(cells/L)	$< 1 \times 10^9$	
Lymphocyte Count		
(cells/mm^3)	< 500	
(cells/L)	$< 0.5 \times 10^9$	
Eosinophil Count		
(cells/mm^3)		> 5,000
(cells/L)		$> 5 \times 10^9$
aPTT		> 2 × ULN
International Normalized Ratio		> 2 × ULN

Table 6. Criteria for Potentially Clinically Significant Chemistry Values

Test/Units	Very Low (VL)	Very High (VH)
ALT/SGPT		> 5 × ULN and ≥ 2 × baseline
AST/SGOT		> 5 × ULN and ≥ 2 × baseline
Alkaline Phosphatase		> 1.5 × ULN
Total Bilirubin (mg/dL)		≥ 2.0 × ULN
Creatinine		
(mcmol/L)		≥ 132.605
(mg/dL)		≥ 1.5
Creatinine Clearance (mL/min)	< 50	
BUN		> 5 × ULN
Uric Acid		
(mcmol/L)		> 713.817
(mg/dL)		> 12.0
Phosphate		
(mmol/L)	< 0.6	
(mg/dL)	< 2.0	
Calcium, Serum		
(mmol/L)	< 1.75	> 3.1
(mg/dL)	< 7.0	> 12.5
Calcium, Ionized (mmol/L)	< 0.9	> 1.6
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 6. Criteria for Potentially Clinically Significant Chemistry Values (Continued)

Test/Units	Very Low (VL)	Very High (VH)
Protein		
(g/L)	< 50	
(g/dL)	< 5.0	
Cholesterol		
(mmol/L)		> 10.34
(mg/dL)		> 400
Triglycerides		
(mmol/L)		> 5.7
(mg/dL)		> 500

11.3.2 Statistical Methods

Mean changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized for each protocol-specified laboratory parameter, including IP-10, with the baseline mean, visit mean, change from baseline mean, standard deviation, and median.

Laboratory data values, excluding IP-10, 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 (related to the normal range), maximum value (related to the normal range) and final values during DAA treatment (DAA Study Drug End Day ≤ 2) will be created. The shift tables 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 shift tables will also cross tabulate the frequency and percentage of subjects with baseline values below/within the normal range versus minimum/maximum/final values below/within/above the normal range. The shift tables will also cross tabulate the frequency and percentage of subjects with baseline values within/above the normal range versus minimum/maximum/final values below/within/above the normal range.

Frequencies and percentages of subjects with post-baseline chemistry and hematology values during DAA treatment (DAA Study Drug End Day ≤ 2) meeting criteria for Potentially Clinically Significant (PCS) Laboratory Values (Table 5 and Table 6) will be summarized. A post-baseline value must be more extreme than the baseline value to be considered as a PCS finding. Listings will be provided that presents all of the subjects and values meeting the PCS criteria (at any time during the study).

For the liver function tests of ALT and AST, the frequency and percentage of subjects with a maximum CTCAE Grade of 1, 2, 3, or 4 (see definitions in Table 8) at any post-nadir visit (regardless of the baseline value) through the end of DAA treatment (DAA Study Drug End Day ≤ 2) will be summarized. For hemoglobin, creatinine clearance, alkaline phosphatase, and total bilirubin, the frequency and percentage of subjects with a maximum CTCAE Grade of 1, 2, 3, or 4 (see definitions in Table 7) at any post-baseline visit (regardless of the baseline value) through the end of DAA treatment (DAA Study Drug End Day ≤ 2) will be summarized. The summaries will include rows for the number and percentage of subjects with at least Grade 2 and at least Grade 3 laboratory abnormalities. Accompanying listings of all ALT, AST, total, indirect and direct bilirubin, and alkaline phosphatase (as available) will be created for any subject who had at least a Grade 3 ALT, AST, alkaline phosphatase, or total bilirubin. A similar listing will be provided for hemoglobin that includes all hemoglobin, total neutrophils, platelet count, and WBC values and for creatinine clearance that includes creatinine clearance, eGFR and creatinine values.

Table 7. Definitions of CTCAE Grades 1, 2, 3, and 4 for Liver Function Tests and Hematology

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
Creatinine clearance (Cockcroft Gault calculation)	< LLN – 60 mL/min	< 59 – 30 mL/min	< 29 – 15 mL/min	< 15 mL/min

The number and percentage of subjects meeting the following criteria during Substudy 1 [i.e., through the end of DAA treatment (DAA Study Drug End Day ≤ 2)] will be summarized:

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

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

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

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

The Criteria for Potentially Clinically Significant Vital Sign Values are presented in Table 8.

Table 8. Criteria for Potentially Clinically Significant Vital Sign Values

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

11.4.2 Statistical Methods

Vital signs will be summarized at each visit in the TI, PR, and Post Treatment Periods. 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 TI, PR, and Post Treatment Periods.

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

Frequencies and percentages of subjects with post baseline values during DAA treatment (DAA Study Drug End Day ≤ 2) meeting Criteria for Potentially Clinically Significant Vital Signs values (Table 8) will be summarized. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A separate listing will be provided that presents all of the subjects and values meeting PCS criteria (at any time during the study).

12.0 Summary of Changes

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

- Remove history of bleeding disorders, tobacco and alcohol use status and treatment during the gap between the prior study and Study M13-101 from demographic and baseline characteristics summary (see Section 7.1).
- Add sensitivity analysis of SVR_{12} using a Modified Intent-to-Treat Genotype and Virologic Failure (mITT-GT + VF) population (see Section 10.4).
- The list of signature amino acid positions important for the NS3/4A protease and NS5A inhibitor class were updated for resistance analyses (see Section 10.6).
- Change "EOTR" to "Final Treatment Visit Response" to avoid confusion with the definition of "EOTR" in other HCV studies with DAA regimens not including pegIFN and change "rebound" to "breakthrough" to align with terminology in newer HCV studies.
- Remove EVR, $SVR_{12planned}$, $SVR_{24planned}$, and Kaplan-Meier curves of the time to suppression and the time to relapse from additional efficacy endpoints to be consistent with analysis plans for newer HCV studies.
- Remove logistic regression to explore potential predictors of response due to the small sample size of the study.
- Replace exact binomial method with Wilson score method for confidence interval calculation.
- Remove summaries of baseline characteristics and efficacy endpoints by treatment in previous study. Add SVR_{12} subgroup analysis by treatment in previous study.

13.0 Reference

1. Wilson EB. Probable inference, the law of succession, and statistical inference. J Amer Statist Assoc. 1927;22:209-12.
2. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.
3. National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4, Available on the Cancer Therapy Evaluation Program (CTEP). Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Document Approval

Study M13101 - Statistical Analysis Plan Version 1 - 05May2017 (E3 16.1.9)

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Signed by:	Date:	Meaning Of Signature:
[redacted]	08-May-2017 02:42:21 PM	Approver
	08-May-2017 02:57:22 PM	Approver
	08-May-2017 09:00:24 PM	Author
	08-May-2017 10:35:16 P	Approver

16.1__9.2 CMQ Preferred Terms

The AbbVie, Hepatic Decompensation and Hepatic Failure, company MedDRA query included the following preferred terms:

Preferred Terms in the AbbVie Hepatic Decompensation and Hepatic Failure MedDRA (Version 19.0) Query
Acute hepatic failure
Acute on chronic liver failure
Anorectal varices haemorrhage
Ascites
Bacterascites
Coma hepatic
Drug-induced liver injury
Gastric varices haemorrhage
Hepatic encephalopathy
Hepatic failure
Hepatic hydrothorax
Hepatorenal failure
Hepatorenal syndrome
Intestinal varices haemorrhage
Liver transplant
Minimal hepatic encephalopathy
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Peritonitis bacterial
Subacute hepatic failure