## 1.0 Title Page

NCT02292

# Statistical Analysis Plan

## Study M14-567

## A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of the Co-Administration of Ombitasvir/ABT-450/Ritonavir (Ombitasvir/ABT-450/r) With Sofosbuvir (SOF) With or Without Ribavirin (RBV) in Subjects With Genotype 2 Chronic Hepatitis C Virus (HCV) Infection or Genotype 3 HCV Infection With or Without Cirrhosis

## Date: 12 Jul 2017

## Version 2.0

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# 3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by AbbVie Statistics and Statistical Programming for Study Protocol M14-567.
Study M14-567 examines the safety and efficacy of co-administration of ombitasvir/ABT-450/ritonavir (r) with sofosbuvir (SOF) with and without ribavirin (RBV) in adults with genotype 3 chronic hepatitis C virus (HCV) infection with and without cirrhosis for 12 weeks, and genotype 2 HCV infection without cirrhosis for 8 and 6 weeks.

This SAP provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work for both the interim analyses (after all subjects in Arm A and Arm B reach Post-Treatment [PT] Week 12 or permanently discontinue the study, after all subjects in Arm C, D, E and F reach PT Week 12 or permanently discontinue the study) and the final analysis (at the end of study). Analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system.

# 4.0 Study Objectives, Design and Procedures

## 4.1 Objectives

The primary objectives of this study are to assess the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response, $SVR_{12}$ [HCV ribonucleic acid {RNA} < lower limit of quantification {LLOQ} 12 weeks following treatment]) of co-formulated ombitasvir with ABT-450/r (ombitasvir/ABT-450/r) co-administered with sofosbuvir (SOF) with or without ribavirin (RBV) for 12 weeks in HCV genotype 3-infected adult subjects with and without cirrhosis, and 8 and 6 weeks in HCV genotype 2-infected adult subjects without cirrhosis.

The secondary objectives of this study are to assess the percentage of subjects with on treatment virologic failure and the percentage of subjects with relapse post-treatment (PT), and characterize the pharmacokinetics of direct-acting antiviral agents (DAAs)

including ombitasvir/ABT-450/r, SOF, GS-331007 (predominant circulating metabolite of SOF), and RBV (if applicable).

## 4.2 Design Diagram

This is a Phase 2, randomized, open-label, multicenter study evaluating the efficacy and safety of co-administration of ombitasvir/ABT-450/r with SOF with or without RBV administered for 12 weeks in HCV GT3 (with and without cirrhosis) and 8 and 6 weeks for GT2 (without cirrhosis) infected, treatment-naïve and treatment-experienced (previous pegIFN/RBV and/or SOF) adults. Approximately 70 subjects will be enrolled at approximately 8 sites globally.

**Treatment Period and Post-Treatment Period**

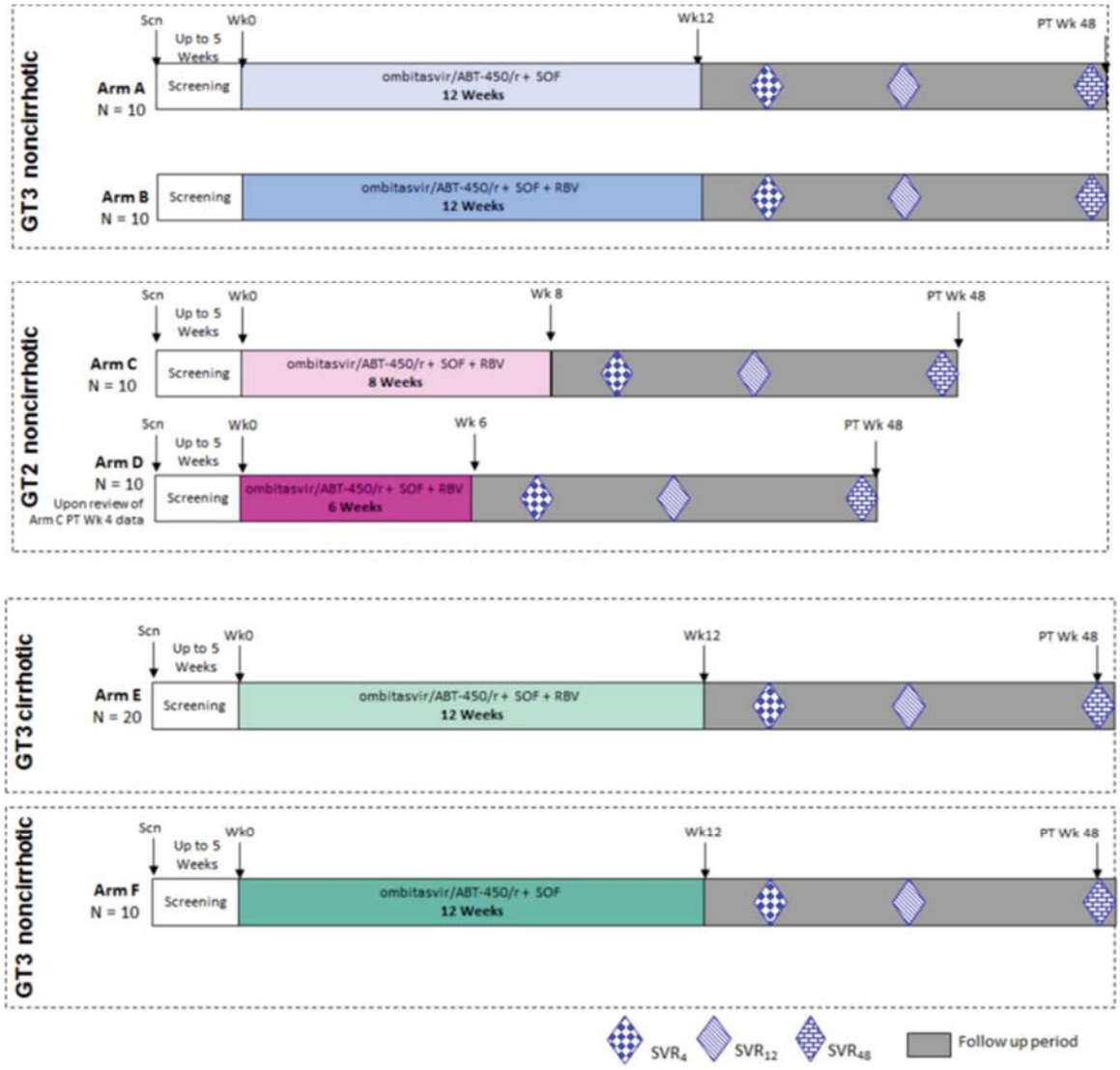
Approximately 20 GT3 subjects without cirrhosis meeting the eligibility criteria will be randomized 1:1 into Arm A and Arm B and treated as below:

- Arm A: ombitasvir/ABT-450/ritonavir 25/150/100 mg once daily (QD) and SOF 400 mg (QD) for 12 weeks;
- Arm B: ombitasvir/ABT-450/ritonavir 25/150/100 mg once daily (QD) and SOF 400 mg (QD) with RBV 1000 – 1200 mg divided twice daily (BID) per local label for 12 weeks.

Randomization to Arms A and B will be stratified by IL28B genotype (CC versus non-CC) and prior treatment status (treatment-naïve versus treatment-experienced).

Approximately 10 GT2 subjects meeting the eligibility criteria will be enrolled in to each of Arm C and Arm D and treated as described below. Arm D would be launched if no more than one subject who completes treatment in Arm C experiences relapse through PT Week 4.

**Figure 1. Study Schematic**




- Arm C: ombitasvir/ABT-450/ritonavir 25/150/100 mg once daily (QD) and SOF 400 mg (QD) with weight based RBV 1000 – 1200 mg BID per local label for 8 weeks;

- Arm D: ombitasvir/ABT-450/ritonavir 25/150/100 mg once daily (QD) and SOF 400 mg (QD) with weight based RBV 1000 – 1200 mg BID per local label for 6 weeks;

Approximately 20 subjects with genotype 3 HCV infection with compensated cirrhosis (aminimum of approximately 20% will be treatment-experienced) will be enrolled into Arm E:

- Arm E: ombitasvir/ABT-450/r 25 mg/150 mg/100 mg and SOF 400 mg QD with RBV 1000 – 1200 mg BID for 12 weeks

An additional 10 subjects with genotype 3 HCV infection without cirrhosis will be enrolled in open-label fashion into Arm F:

- Arm F: ombitasvir/ABT-450/r 25 mg/150 mg/100 mg and SOF 400 mg QD for 12 weeks

RBV dosing will be weight-based, either 1000 mg or 1200 mg daily divided BID per local label (e.g., < 75 kg = 1000 mg daily divided BID or ≥ 75 kg = 1200 mg daily divided BID).

Upon completing the Treatment Period (TP) or premature discontinuation of the TP, subjects will enter the PT Period. All subjects who receive at least one dose of study drugs in the TP and either complete treatment or prematurely discontinue study drug will be monitored for an additional 48 weeks in the Post-Treatment Period for safety, HCV RNA, the emergence and/or persistence of resistant viral variants and assessment of patient reported outcomes (PROs). A study schematic is shown in Figure 1. The PT Period will begin the day following the last dose of study drug treatment.

## 4.3 Sample Size

It is planned to enroll approximately 70 subjects into this study. With a sample size of 10 subjects per arm and an observed $SVR_{12}$ rate of 90%, the 2-sided 95% confidence

interval, using Wilson's score confidence interval, will be (59.6%, 98.2%); With a sample size of 20 subjects per arm and an observed $SVR_{12}$ rate of 90%, the 2-sided 95% confidence interval, using Wilson's score confidence interval, will be (69.9%, 97.2%). Subjects who do not have data at PT Week 12 (after performing the described imputation) count as failures for $SVR_{12}$ so no adjustment for dropout is applicable.

From the perspective of safety assessment, the probability that a given adverse event would not be observed among 70 subjects is shown in the second column of Table 1 for various true population incidence rates. With 70 subjects, the probability is at least 99.9% to observe an adverse event with an incidence rate of 10% or higher.

**Table 1. Probability of Not Observing an Adverse Event or Lab Abnormality with 70 Subjects for Various True Incidence Rates**

| True Incidence Rate | Probability of Not Observing |
|---|---|
| 0.10 | < 0.001 |
| 0.20 | < 0.001 |
| 0.30 | < 0.001 |
| 0.40 | < 0.001 |
| 0.50 | < 0.001 |

## 4.4 Planned Analysis

All analyses will be conducted by statisticians and programmers at AbbVie or designee according to the methodologies specified in this SAP. There is no intention of stopping the study early based on efficacy findings from the interim analysis. The intention is to follow all subjects who receive active drugs for defined durations in each arm.

### 4.4.1 Interim Analysis

There will be an interim analysis after all enrolled subjects in Arms A and B have completed through Post-Treatment Week 12 or prematurely discontinued from the study, and another interim analysis after all enrolled subjects in Arms C, D, E and F have

completed through Post-Treatment Week 12 or prematurely discontinued from the study. For interim analyses, data will be locked after performing appropriate data cleaning.

Data collected after each interim analysis will be added to a new version of the database. At the end of the study, all data will be cleaned and locked and included in the final CSR.

# 5.0 Analysis Populations

## 5.1 Definition for Analysis Populations

### 5.1.1 Intent-to-Treat (ITT) Population

All enrolled subjects who receive at least one dose of study drug will be included in the ITT population. Efficacy analyses will be performed on the ITT population.

Modified Intent-to-Treat Population

Sensitivity analyses of the primary endpoint, when applicable, will be performed on the modified ITT (mITT) population to exclude subjects not of genotype as specified in each arm or not of genotype specified in each arm according to phylogenetic analyses (mITT-GT), and on the mITT-GT population further modified to exclude subjects who did not achieve $SVR_{12}$ for reasons other than virologic failure (mITT-GT-VF).

### 5.1.2 Safety Population

All subjects who receive at least one dose of study drug will be included in the safety population. Safety and demographic analyses will be performed on the safety population.

## 5.2 Variables Used for Stratification of Randomization

Approximately 20 HCV genotype 3-infected subjects will be randomized to Arm A or Arm B in a 1:1 ratio. Randomization will be stratified by IL28B genotype (CC versus non-CC) and prior treatment status (treatment-naïve versus treatment-experienced).

There is no randomization for HCV subjects enrolled into Arms C to F.

# 6.0 Analysis Conventions

## 6.1 Baseline and Final Value

### 6.1.1 Baseline

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

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

### 6.1.2 Study Days

Study days (days relative to the first dose of study drug) are calculated for each time point relative to the first dose of study drug. Study Days are negative values when the time point of interest is prior to the first study drug dose day. Study Days are positive values when the time point of interest is after the first study drug dose day. There is no Study Day 0. Study Day 1 is the day of the first dose of study drug.

**Study Drug End Days**

For all subjects who receive at least one dose of study drug, study drug end days (days relative to the last dose of study drug) are calculated relative to the last dose of study drug. The last day of study drug is defined as Study Drug End Day 0. Days before it have negative study drug end days and days after it have positive study drug end days.

**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.

**Final Post-Treatment Value**

The final post-treatment value for each subject is the last non-missing measurement collected after Study Drug End Day 2, and on or before Study Drug End Day 999.

## 6.2 Analysis Windows

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

For visit windows of analyses of health-related quality of life (QoL) patient reported outcomes (PROs) collected throughout the study, Table 6 will be used.

For laboratory data and vital signs, the time windows specified in Table 2, Table 3, Table 4, and Table 7 describe how data are assigned to protocol specified time points during the Treatment and PT Periods.

If more than one assessment is included in a time window, the assessment closest to the nominal time will be used. If there are two observations equally distant to the nominal time, the latest one will be used in analyses. The only exception to this is for the SVR windows (e.g., $SVR_4$, $SVR_{12}$, and $SVR_{24}$); for these windows, the last value in the window will be used.

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

**Table 2. Analysis Time Windows for HCV RNA, Resistance Endpoints, Laboratory Data, and Vital Sign (Treatment Period) for 12-Week of Treatment**

| Scheduled Visit | Nominal Day (Study Day) | Time Window (Study Day Range) |
|---|---|---|
| Day 1/Baseline[a] | 1[a] | ≤ 1[a] |
| Week 1 | 7 | 2 to 10 |
| Week 2 | 14 | 11 to 21 |
| Week 4 | 28 | 22 to 42 |
| Week 8 | 56 | 43 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 |

a. Day of first dose of study drug.

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

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used. Child-Pugh classification (for cirrhotic subjects only), FibroTest are collected at Screening and Week 12 (or upon study discontinuation) and will use those visit windows as defined above. FibroTest is also collected at baseline, only if not performed at the time of screening.

**Table 3. Analysis Time Windows for HCV RNA, Resistance Endpoints, Laboratory Data, and Vital Sign (Treatment Period) for 8-Week of Treatment**

| Scheduled Visit | Nominal Day (Study Day) | Time Window (Study Day Range) |
|---|---|---|
| Day 1/Baseline[a] | 1[a] | ≤ 1[a] |
| Week 1 | 7 | 2 to 10 |
| Week 2 | 14 | 11 to 21 |
| Week 4 | 28 | 22 to 42 |
| Week 8 | 56 | 43 to 70 |
| Final Treatment Visit[b] | | 2 to ≤ 2 days after last dose of study drug |

a. Day of first dose of study drug.

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

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used.

**Table 4. Analysis Time Windows for HCV RNA, Resistance Endpoints, Laboratory Data, and Vital Sign (Treatment Period) for 6-Week of Treatment**

| Scheduled Visit | Nominal Day (Study Day) | Time Window (Study Day Range) |
|---|---|---|
| Day 1/Baseline[a] | 1[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 |
| Final Treatment Visit[b] | | 2 to ≤ 2 days after last dose of study drug |

a. Day of first dose of study drug.

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

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used.

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

| Scheduled Visit[a] | Nominal Day (Study Drug End Day) | Time Window (Study Drug End Day Range) |
|---|---|---|
| Post-Treatment Week 2 | 14 | 3 to 21 |
| Post-Treatment Week 4 | 28 | 22 to 42 |
| Post-Treatment Week 8 | 56 | 43 to 77 |
| Post-Treatment Week 12 | 84 | 78 to 126 |
| Post-Treatment Week 24 | 168 | 127 to 210 |
| Post-Treatment Week 36 | 252 | 211 to 294 |
| Post-Treatment Week 48 | 336 | 295 to 378 |
| $SVR_4$[b] | 28 | 3 to 56 |
| $SVR_{12}$[b] | 84 | 57 to 126 |
| $SVR_{24}$[b] | 168 | 127 to 210 |

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

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

Note: The result closest to the scheduled time point will be used, except for $SVR_4$, $SVR_{12}$, and $SVR_{24}$. Data must also have Study Drug End Day > 2 for all windows. Study Drug End Day 0 is defined as the day of the last dose of study drug.

## Table 6. Analysis Time Windows for PRO Instruments

| Scheduled Visit | Nominal Day (Study Day) | Time Window (Study Days Range) |
|---|---|---|
| 12-Week Treatment | | |
| Day 1/Baseline | 1[a] | ≤ 1[a] |
| 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 |
| 8-Week Treatment | | |
| Day 1/Baseline | 1[a] | ≤ 1[a] |
| Week 4 | 28 | 2 to 42 |
| Week 8 | 56 | 43 to 70 |
| Final Treatment Visit[b] | | 2 to ≤ 2 days after last dose of study drug |
| 6-Week Treatment | | |
| Day 1/Baseline | 1[a] | ≤ 1[a] |
| Week 4 | 28 | 2 to 35 |
| Week 6 | 42 | 36 to 49 |
| 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 | 168 | 127 to 252 |
| Post-Treatment Week 48 | 336 | 253 to 378 |
| Final Post-Treatment Visit[c] | | > 2 days after last dose of study drug |

a. Day of first dose of study drug.

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

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

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

**Table 7. Laboratory Data and Vital Sign Visit Windows (Post-Treatment Period)**

| Scheduled Time | Nominal Day (Study Drug End Day) | Time Window (Study Drug End Days Range) |
|---|---|---|
| Post-Treatment Week 2 | 14 | 3 to 21 |
| Post-Treatment Week 4 | 28 | 22 to 42 |
| Post-Treatment Week 8 | 56 | 43 to 77 |
| Post-Treatment Week 12 | 84 | 78 to 126 |
| Post-Treatment Week 24 | 168 | 127 to 210 |
| Post-Treatment Week 36 | 252 | 211 to 294 |
| Post-Treatment Week 48 | 336 | 295 to 999 |
| Final Post-Treatment Visit[a] | | > 2 days after last dose of study drug |

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

Note: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day > 2. Vital signs are collected at every Post-Treatment Period visit. Hematology, chemistry, urinalysis, and coagulation panels are collected at Post-Treatment Week 4 and 12 and will use visit windows defined above. Child-Pugh classification, fibro test are collected at Post-Treatment Week 12 and 48 (or upon study discontinuation) and will use those visit windows as defined above.

## 6.3 Missing Data Imputation

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

HCV RNA values will be selected for the $SVR_{12}$ analysis based on defined visit windows. When there is no HCV RNA value in a visit window based on defined visit windows, the closest values before and after the window, regardless of the value chosen for the subsequent and preceding window, will be used for the flanking imputation described below.

If a subject has a missing HCV RNA value at a post-Day 1 visit, but with undetectable or unquantifiable HCV RNA levels at both the preceding value and succeeding value, the HCV RNA level will be considered undetectable or unquantifiable, respectively, at this visit for this subject. For $SVR_{12}$ analysis, if there is no value in the appropriate window

after flanking imputation but there is an HCV RNA value after the window, then it will be imputed into the $SVR_{12}$ window. Similarly, for $SVR_{24}$ analysis, if there is no value in the appropriate window after flanking imputation but there is HCV RNA value after the window, then it will be imputed into the $SVR_{24}$ window.

If a subject starts another treatment for HCV, then all HCV RNA and PRO values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses. The subject will be considered a failure for summaries of viral response at all time points after the start of the new HCV treatment.

HCV RNA < LLOQ Analyses for SVR

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

HCV RNA Analyses for Relapse and Virologic Failure

If HCV RNA values from the central laboratory are missing but a local laboratory value is present in the appropriate time period, then the local laboratory value will be used to assess post-treatment relapse and on-treatment virologic failure.

**Missing Data Imputation for PRO Questionnaires**

The handling of missing data for patient reported outcomes (PROs) will be as follows. The missing items of the FSS questionnaire will be imputed with the average score of the answered items as long as more than 50% of the items on the FSS are answered. For EQ-5D-5L index and VAS scores, no imputation will be performed for missing items.

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

Demographics, baseline characteristics, medical history, and previous/concomitant medications will be summarized for the safety population.

## 7.1 Demographic and Baseline Characteristics

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

Baseline characteristics will include: IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), prior treatment history (treatment naïve, pegIFN/RBV null-responder, pegIFN/RBV partial responder, SOF breakthrough/nonresponder, HCV therapy relapser, HCV relapse/breakthrough, HCV therapy nonresponder, pegIFN intolerant, and pegIFN experienced), baseline HCV RNA levels ([continuous (use $log_{10}$ HCV RNA)] and [< 800,000 IU/mL or ≥ 800,000 IU/mL]), baseline HOMA-IR (< 3 or ≥ 3 mU × $mmol/L^2$), baseline IP-10 category (< 600 or ≥ 600 ng/L), baseline albumin (continuous), baseline albumin (< 35, ≥ 35 g/L), baseline platelet count (continuous, and < 90 × $10^9$/L, ≥ 90 × $10^9$/L), baseline alpha fetoprotein (continuous, and < 20 ng/mL, ≥ 20 ng/mL), baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, or F4), Child Pugh score (5, 6, or > 6), FibroTest Score, tobacco (user, ex-user, or non-user) and alcohol (drinker, ex-drinker, or non-drinker) use status, history of diabetes, history of depression or bipolar disorder, history of hypertension, and history of cardiovascular disease other than hypertension.

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

Baseline Child-Pugh score is determined by the Day 1 assessment of ascites and hepatic encephalopathy along with the baseline values of total bilirubin, serum albumin, and international normalized ratio (INR). The Child-Pugh score is the sum of the point assigned for each of the five observed findings as defined in Table 8.

**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.

Baseline fibrosis stage is defined for subjects with non-missing liver biopsy scores, FibroScan scores, or FibroTest scores. Only one score will be used to categorize each subject even if a subject has more than one score recorded. If a biopsy score is present, then it will be used to categorize the subject, regardless of the FibroScan/FibroTest score. Similarly, if a FibroScan score is present along with a FibroTest score, then the FibroScan score will be used to categorize the subject. If biopsy and FibroScan scores are not present and more than one FibroTest result is available, then the Baseline FibroTest result (i.e., last non-missing FibroTest result on or before Day 1) will be used to categorize the subject. Subjects will be categorized as F0 – F1, F2, F3, or F4 according to Table 9.

**Table 9. Baseline Fibrosis Stage**

| Baseline Fibrosis Stage, Metavir Equivalents | Liver Biopsy Metavir, Batts-Ludwig, Knodell, IASL, Scheuer, 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 |

Summary statistics (N, mean, median, standard deviation (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., sex and race).

## 7.2 Medical History

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

## 7.3 Previous Treatment and Concomitant Medications

Prior and concomitant medications will be summarized. A prior medication is defined as any medication taken prior to the date of the first dose of study drug (Ombitasvir/ABT-450/r or SOF). A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last (maximum) dose of study drug. Concomitant medications will be summarized for all subjects in the Safety population. The number and percentage of subjects taking prior or concomitant medications will be

summarized by generic drug name based on the WHO Drug Dictionary. Note that prior HCV medications (pegIFN and RBV, SOF) will be summarized separately from other prior medications.

Medications for the treatment of HCV will be collected in the PT Period and will be summarized for each treatment arm by generic drug name. A post-treatment medication for the treatment of HCV is defined as any medication taken on or after the last (maximum) dose of study drug and entered as "Post treatment HCV medications" on the eCRF.

# 8.0 Patient Disposition

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

- Randomized subjects;
- Subjects who took at least one dose of study drug;
- Subjects who completed study drug;
- Subjects who discontinued from study drug;
- Subjects who completed the study;
- Subjects who discontinued from the study.

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

The number and percentage of all subjects as applicable will be summarized by treatment arm for:

- Subjects with interruptions of all study drugs for toxicity management;
- Subjects with any RBV dose modifications;
    - Subjects with RBV dose modification due to decrease in hemoglobin;

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

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

# 9.0 Study Drug Exposure and Compliance

## 9.1 Exposure

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

The safety population will be used to summarize the duration of exposure for each treatment arm.

Descriptive statistics (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
- 76 to 90 days
- > 90 days

In addition, the number and percentage of subjects with a study drug duration of ≥ 77 days for Arm A, B, E and F, ≥ 49 days for Arm C, and ≥ 38 days for Arm D will be summarized.

### 9.2 Compliance

At each protocol-specified visit, the total number of tablets dispensed and returned is recorded for each type of study drug. The compliance for each study drug (Ombitasvir/ABT-450/r, SOF, and RBV, if applicable) within the Treatment Period will be calculated as the percentage of tablets taken relative to the total tablets, respectively, expected to be taken. The total number of tablets prescribed will be equal to the total number of tablets that should have been taken per the protocol for the duration that the subject was in the Treatment Period (date of last dose – date of first dose + 1 day). Study drug interruptions due to an adverse event or other planned interruptions recorded on the eCRF will be subtracted from the duration. A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum. In addition, the percentage of compliant subjects will be calculated for each study drug and each treatment arm.

## 10.0 Efficacy Analysis

### 10.1 General Considerations

Analyses will be performed on the intent-to-treat (ITT) population. Sensitivity analyses of the primary endpoint, when applicable, will be performed on the mITT-GT-VF population specified in Section 5.1.1.

Missing data will be imputed as described in Section 6.3 for analyses of the HCV RNA endpoints of SVR.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-

PCR) assay v.2.0. For this assay, the lower limit of quantitation (LLOQ) is 25 IU/mL regardless of genotype, and the lower limit of detection (LLOD) varies by genotype. For GT3, the lower limit of detection (LLOD) is 20 IU/mL; for GT2, LLOD is 20 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.

IL28B rs12979860 will be resulted as C/C, C/T, or T/T by the central laboratory.

**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.

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

**On-treatment virologic failure** = breakthrough or failure to suppress during treatment (all on-treatment values of HCV RNA ≥ LLOQ) with at least 6 weeks (defined as study drug duration ≥ 36 days) of treatment for 12-week and 8-week treatment or at least 26 days of treatment for 6-week treatment.

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

**EOTR** (end of treatment response) = HCV RNA < LLOQ in the Week 12 window for 12-week regimen, Week 8 window for 8-week regimen, and Week 6 for 6-week regimen.

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

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

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

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

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

**$Relapse_{late}$** = 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, excluding re-infection.

**$Relapse_{overall}$** = 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. Completion of treatment is defined as a study drug duration ≥ 37 days, ≥ 49 days and ≥ 77 days for planned treatment duration of 6 week, 8 weeks and 12 week, respectively. Also, include a

summary of $Relapse_{overall}$ for subjects who prematurely discontinued treatment, excluding re-infection.

For relapse analyses, the completion of treatment is defined as above. If the last available post-treatment value is ≥ LLOQ, then the subject will be considered a relapse (i.e., will not require confirmation). Relapse analyses will exclude subjects who do not have any post-treatment HCV RNA values.

HCV re-infection is defined as confirmed HCV RNA ≥ LLOQ after the end of treatment in a subject who had HCV RNA < LLOQ at Final Treatment Visit, along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis of the NS3 or NS5A, and/or NS5B gene sequences. Re-infection in the case of the same HCV subtype is defined as a clade switch, as indicated by the lack of clustering between the baseline and post-treatment sequences by phylogenetic analysis. If phylogenetic analysis is not possible due to technical difficulties, HCV re-infection may be determined with a confirmed HCV genotype or subgenotype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

**Reasons for $SVR_{12}$ Non-Response**

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

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. Relapse (defined according to the **$Relapse_{12}$** definition for subjects who complete treatment);
3. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any $SVR_{12}$ non-responder who prematurely discontinued study drug (duration < 77 days, < 49 days, and < 38 days for 12 week, 8 week, and 6 week treatment regimens) and did not meet the **On-treatment virologic failure definition**);

4. HCV re-infection (see definition described earlier);
5. Missing follow-up data in the $SVR_{12}$ window (defined as any subject who completed study drug without data in the $SVR_{12}$ window and not meeting the definitions of [1], [2], [3], or [4]);
6. Other (defined as any $SVR_{12}$ non-responder not meeting the definitions of [1] – [5], such as a subject with a single quantifiable value within the $SVR_{12}$ window followed by an undetectable value beyond the $SVR_{12}$ window).

**Reasons for $SVR_{24}$ Non-Response**

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

1. On-treatment virologic failure (see **On-treatment virologic failure definition**);
2. Relapse (defined according to the **$Relapse_{12}$** definition for subjects who complete treatment);
3. Relapsed after achieving $SVR_{12}$ (see **$Relapse_{24}$**);
4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any $SVR_{24}$ non-responder who prematurely discontinued study drug [duration < 154 days] and did not meet the **On-treatment virologic failure, $Relapse_{12}$**, or **$Relapse_{24}$** definitions);
5. HCV re-infection;
6. Missing follow-up data in the $SVR_{24}$ window (defined as any subject who completed study drug without data in the $SVR_{24}$ window, and not meeting the definitions of [1], [2], [3], [4], or [5]);
7. Other (defined as any $SVR_{24}$ non-responder not meeting the definitions of [1] – [6]).

## 10.2 Handling of Multiplicity

No multiplicity issue applicable in this study.

## 10.3 Primary Efficacy Analysis

The primary endpoint is the percentage of subjects with $SVR_{12}$ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The number and percentage of subjects achieving $SVR_{12}$ will be calculated for each treatment arm and 2-sided 95% Wilson score confidence intervals for a binomial proportion will be computed by treatment arm.

## 10.4 Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- The percentage of subjects in each treatment arm and across all treatment arms with on-treatment virologic failure (breakthrough defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, or confirmed increase from nadir in HCV RNA at any time point during treatment, 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 for 12-week and 8-week treatment or at least 26 days of treatment for 6-week treatment.
- The percentage of subjects with post-treatment relapse ($relapse_{12}$ defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug (up to and including the $SVR_{12}$ assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment. Completion of treatment is defined as study drug duration ≥ 77 days, 49 days and 38 days for 12-week, 8-week, and 6-week of treatment, respectively.

The numbers and percentages of the subjects with virologic failure during treatment and with post-treatment relapse will be calculated for each arm. The corresponding 2-sided 95% Wilson score confidence intervals for a binomial proportion will be calculated.

## 10.5 Sensitivity Analysis

A sensitivity analysis for the primary efficacy endpoint as described in Section 10.3 will be conducted using mITT-GT-VF population defined in Section 5.1.1.

## 10.6 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized and analyzed for each treatment arm:

- All reasons for not achieving $SVR_{12}$ for subjects who do not achieve $SVR_{12}$;
- Number and percentage with unquantifiable HCV RNA at each post-baseline visit throughout the Treatment Period (using data from the central laboratory as observed, i.e., no imputation for missing data);
- The percentage of subjects with HCV RNA < LLOQ 24 weeks after the last actual dose of study drug ($SVR_{24}$);
- All reasons for not achieving $SVR_{24}$ for subjects who do not achieve $SVR_{24}$.
- Time to suppression of HCV RNA (defined as the study day of the first of two successive HCV RNA < LLOQ) during the Treatment Period.

In the above analyses that use the number and percentage of responders, the rates and 2-sided 95% Wilson score confidence interval for a binomial proportion will be calculated.

For HCV RNA levels, the time to suppression during treatment will be calculated for each subject, and the median time will be estimated using Kaplan-Meier methodology for right censored observations.

Imputations for missing data will be performed as described in Section 6.3 for analyses of SVR, RVR, and EOTR where a missing response will be imputed as a failure after performing the described imputation. All other endpoints will be presented using data as observed.

The number and percent of subjects who fail to suppress HCV RNA and received at least 6 weeks of treatment (active study drug duration ≥ 38 days) will be tabulated along with the subject numbers corresponding to the subjects who failed to suppress.

The number of subjects who breakthrough at any time during treatment and within each protocol-specified visit (defined in Table 2, Table 3, and Table 4) will be summarized along with a corresponding listing displaying the subject numbers at the first occurrence of breakthrough.

The number of completers (defined as study drug duration ≥ 77 days, ≥ 49 days, ≥ 38 days for 12-week, 8-week, 6-week of treatment, respectively) with final on treatment HCV RNA < LLOQ who relapse within the $SVR_4$ window, within the $SVR_{12}$ window, within the $SVR_{24}$ window (defined in Table 5), and anytime post-treatment (study drug end day ≥ 3) will be summarized along with a corresponding listing displaying the first occurrence of relapse. A similar table and listing will be provided of Preterm Relapses for subjects who do not complete treatment (defined as study drug duration < 77 days, < 49 days, < 38 days for 12-week, 8-week, 6-week of treatment, respectively) with HCV RNA < LLOQ at the Final Treatment visit.

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

## 10.7 Resistance Analyses

If possible, subjects treated with study drug during the Treatment Period who experience virologic failure will have resistance testing conducted if 1) they have on-treatment

breakthrough; 2) if they have post-treatment relapse (irrespective of the time of relapse), with a study drug duration ≥ 77 days, 49 days and 38 days for 12-week, 8-week, and 6-week of treatment, respectively; or 3) if they have at least 6 weeks of treatment and fail to suppress by Week 6 (i.e., meet virologic stopping criteria). Subjects meeting one of these criteria will be referred to as subjects in the primary virologic failure (PVF) population, and a listing by subject that includes HCV subtype, IL28B genotype, reason for non-response, time point(s) sequenced as closest to time of VF, and HCV RNA value at the VF time point(s) will be produced for these subjects. In addition, all listings described below will display HCV subtype and reason for non-response in the subject identifier for each subject. A separate listing will delineate all subjects in the PVF population for whom no sequencing was performed (e.g., lost to follow-up while HCV RNA ≤ 1000 IU/mL). Subjects treated with study drugs who do not achieve $SVR_{12}$ who do not meet the above criteria for the PVF population (e.g., those with less than 6 weeks of therapy who failed to suppress), but have a time point with HCV RNA ≥ 1000 IU/mL after treatment discontinuation, will have the sample at that time point sequenced.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore if the HCV RNA level at the time of virologic failure (VF) or treatment discontinuation is < 1000 IU/mL, the sample closest in time after the failure/discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used if available. Next generation sequencing (NGS) of a given target will be performed only if no variants are detected at signature amino acid positions by population sequencing in that sample. Included time points for analyses on subjects in the PVF and non-PVF population are: 1) time of virologic failure/treatment discontinuation or sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1,000 IU/mL, 2) 24 weeks post-DAA treatment, provided that resistance-associated variants were detected by either population sequencing or NGS at the time of failure/discontinuation, and 3) 48 weeks post-DAA treatment, provided that resistance-associated variants were detected by either population sequencing or NGS at 24 weeks post-DAA treatment. For these samples, NGS will be performed on a given target only if no variants are detected at signature amino acid positions by population sequencing.

The regions of interest for population sequencing and NGS for all samples from subjects who do not achieve $SVR_{12}$ are those encoding complete NS3/4A, NS5A, and NS5B. The regions encoding NS3 amino acids 1 – 181, NS5A amino acids 1 – 215, and NS5B amino acids 1 – 591 will be sequenced for analysis of baseline samples from the SVR-achieving subjects. An appropriate prototypic reference sequence will be used for comparison with sequences from samples.

The following are considered signature amino acid positions in genotypes 2 and 3: 36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3 only), 168 in NS3; 24, 28, 29, 30, 31, 32, 58, 92, 93 in NS5A; and 142, 159, 237, 282, 289, 320, 321 in NS5B.

The following definitions will be used in the resistance analyses:

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

Analysis will be performed separately for each HCV subtype and study arms within each listing.

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

- A listing of all baseline variants at signature amino acid positions for each DAA target (NS3, NS5A and NS5B) (ITT population).
- Listing of all baseline variants at non-signature amino acid positions for subjects in PVF population.
- The number and percentage of subjects with each baseline variant at a signature amino acid position within each target out of the total number of baseline samples that were sequenced will be provided (ITT population). This table includes prevalence of each baseline variant, and a summary of number of subjects with variants in NS3 only, in NS5A only, in NS5B only, any in NS3, any in NS5A, any in NS5B, any in NS3 or NS5A or NS5B, any in NS3 + NS5A, any in NS3 + NS5B, any in NS5A + NS5B, any in NS3 + NS5A + NS5B.

**Analysis 2:** The impact of baseline variants on treatment outcome will be assessed as follows: for each variant, the $SVR_{12}$ rate will be calculated for subjects with and without the variant and the 2 rates will be compared using Fisher's exact test. Subjects in the non-PVF population will be excluded from this analysis. Analysis will be grouped by (1) study Arm, (2) HCV subtype, (3) DAA target (NS3, NS5A or NS5B).

- Variants at signature amino acid positions (vs no variant at that position).
- Each variant at signature amino acid position (vs not that variant).
- Variants at non-signature amino acid positions (vs no variant at that positions).

**Analysis 3:** The following analyses will be performed for subjects in the PVF and non-PVF populations who have post-baseline resistance data available.

For analysis by population sequencing, the following tables will be provided:

- Listings by subject of all post baseline variants relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A and NS5B).
- Listings by subject of all emerged variants, by amino acid position and variants within a DAA target in a post-baseline sample relative to the baseline amino acid sequence will be provided for each DAA target.

- Listings by subject of all post-baseline variants at signature amino acid positions relative to the appropriate prototypic reference amino acid sequences will be provided for each DAA target (NS3, NS5A and NS5B).
- A listing by subject and time point of the linked variants by population sequencing for each target will be provided.

For analysis by NGS, the following tables will be provided:

- Listings by subject of all variants at signature amino acid positions in a post-baseline time point for each DAA target (NS3, NS5A and NS5B).

## 10.8 Patient Reported Outcomes

The following instruments will be used to collect patient reported outcomes (PROs): EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) and Fatigue Severity Scale (FSS). Missing data for each measurement will be handled as described in Section 6.3.

The following exploratory analyses of PROs will be performed:

- mean change from baseline in EQ-5D-5L health index score and its VAS score to each applicable post-baseline time point;
- mean change from baseline in the FSS score and its VAFS score to each applicable post-baseline time point.

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). The VAS score will be measured separately.

The FSS measures the impact of fatigue over the past week on specific types of functioning. The survey consists of 9 questions using a 7-point Likert scale. A total score

is calculated as the average of the individual item responses (adding up all the answers and dividing by nine). Subjects also rate their perception of their fatigue on a separate visual analogue fatigue scale (VAFS). Higher FSS scores indicate a higher degree of impact of fatigue.

Summary statistics (n, mean, SD, median, minimum and maximum) for the mean change from baseline to each applicable visit will be provided for the EQ-5D-5L index and its VAS scores, the FSS score and its VAFS scores.

# 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 for each treatment arm using the safety population.

## 11.2 Analysis of Adverse Events

### 11.2.1 Treatment-Emergent Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of study drug through 30 days after the last dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent, unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

#### 11.2.1.1 Tabulations of Treatment-Emergent Adverse Events

Adverse event data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) by treatment arm according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The

actual version of the MedDRA coding dictionary used will be noted in the clinical study report. The system organ classes will be presented in alphabetical order and the preferred terms will be presented in alphabetical order within each system organ class.

**Adverse Event Overview**

An overview of adverse events will be presented consisting of the number and percentage of subjects experiencing at least one event for the following adverse event categories:

- Any treatment-emergent adverse event;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs (Ombitasvir/ABT-450/r);
- Treatment-emergent adverse events with a "reasonable possibility" of being related to RBV (applicable for RBV-containing arms);
- Severe treatment-emergent adverse events;
- Serious treatment-emergent adverse events;
- Treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent adverse events leading to interruption of study drug;
- Treatment-emergent adverse events leading to RBV dose modification (applicable for RBV-containing arms);
- Treatment-emergent adverse events leading to death;
- Deaths.

The adverse event overview summary will be provided for each treatment arm.

**Adverse Event by SOC and PT**

The following summaries of adverse events will be generated by treatment arm:

- Treatment-emergent adverse events;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs (Ombitasvir/ABT-450/r);

- 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").

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

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

**Adverse Event by PT**

The number and percentage of subject experiencing treatment-emergent adverse events will be tabulated according to preferred term and sorted by overall frequency for the total number of subjects in each treatment arm. 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. These summaries will display for each treatment group and be sorted by overall total.

**Adverse Event of Special Interest**

Specific treatment-emergent adverse events of special interest, which may be searched using Standardized or Company MedDRA Queries, will be summarized and include severe cutaneous reactions and anemia. The search criteria for the adverse event of interest are as follows:

- Severe Cutaneous Reactions
  SMQ "Severe cutaneous adverse reactions" (narrow search)
- Anemia
  SMQ "Haematopoietic erythropenia" (broad search) plus the following preferred terms:
  Haemolytic anaemia,
  Coombs negative haemolytic anaemia,
  Coombs positive haemolytic anaemia.

For each adverse event of interest (severe cutaneous reactions and anemia), 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 for each treatment arm and overall and by SOC and PT.

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

**Adverse Event by Maximum Severity**

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

**Adverse Events by Maximum Severity Grade Level**

Treatment-emergent adverse events will be summarized by maximum severity grade level of each preferred term. Each preferred term will be assigned to a grade level based on severity and seriousness, adapted from the Division of AIDS (DAIDS) table for grading severity of adverse events. All serious adverse events will be categorized as Grade 4. Nonserious adverse events categorized by the investigators as mild, moderate, or severe will be categorized as Grade 1, Grade 2, or Grade 3, respectively. If a subject has a nonserious adverse event with unknown severity, then the subject will be counted in the severity grade level category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Grade 3" category. Similarly, if a subject has an adverse event with unknown seriousness, then the subject will be counted in the severity grade level category of "unknown" unless the subject has another occurrence of the same adverse event that is marked serious. In this case, the subject will be counted under the "Grade 4" category.

**Adverse Event by Maximum Relationship**

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

### 11.2.2 Listing of Adverse Event

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

## 11.3 Analysis of Laboratory Data

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

### 11.3.1 Variables and Criteria Defining Abnormality

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

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, serum glutamic pyruvic transaminase (SGPT/ALT), serum glutamic oxaloacetic transaminase (SGOT/AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, uric acid, cholesterol, total protein, glucose, triglycerides, albumin, chloride, bicarbonate, magnesium, gamma glutamyl transferase (GGT), and creatinine clearance (Cockcroft-Gault calculation), calculation of estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation as defined below, alpha2-macroglobulin, haptoglobin, and apolipoprotein A1.

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

Additional variables are total insulin and IP-10.

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

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

The central lab calculates the estimated creatinine clearance (CrCl) based on the following Cockcroft-Gault formula:

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

The Criteria for Potentially Clinically Significant (PCS) Laboratory Findings are described in Table 10 and Table 11. Note that a post-baseline value must be more extreme than the baseline value to be considered a PCS finding.

**Table 10. Criteria for Potentially Clinically Significant Hematology Values**

| Test/Units | Very Low (VL) | Very High (VH) |
|---|---|---|
| Hemoglobin | | |
| (mmol/L) | < 4.9 | |
| (g/dL) | < 8.0 | |
| (g/L) | < 80 | |
| Platelets Count | | |
| (cells/$mm^3$) | < 50,000 | |
| (cells/L) | $< 50 \times 10^9$ | |
| White Blood Cell Count | | |
| (cells/$mm^3$) | < 2000 | > 20,000 |
| (cells/L) | $< 2.0 \times 10^9$ | $> 20 \times 10^9$ |
| Absolute Neutrophil Count | | |
| (cells/$mm^3$) | < 1000 | |
| (cells/L) | $< 1 \times 10^9$ | |
| Lymphocyte Count | | |
| (cells/$mm^3$) | < 500 | |
| (cells/L) | $< 0.5 \times 10^9$ | |
| Eosinophil Count | | |
| (cells/$mm^3$) | | > 5000 |
| (cells/L) | | $> 5 \times 10^9$ |
| aPTT | | > 2 × ULN |
| International Normalized Ratio | | > 2 × ULN |

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

**Table 11. Criteria for Potentially Clinically Significant Chemistry Values**

| Test/Units | Very Low (VL) | Very High (VH) |
|---|---|---|
| ALT/SGPT | | > 5 × ULN and ≥ 2 × baseline |
| AST/SGOT | | > 5 × ULN and ≥ 2 × baseline |
| Alkaline Phosphatase | | > 1.5 × ULN |
| Total Bilirubin (mg/dL) | | ≥ 2.0 × ULN |
| Creatinine | | |
| (mcmol/L) | | ≥ 132.605 |
| (mg/dL) | | ≥ 1.5 |
| Creatinine Clearance (mL/min) | < 50 | |
| BUN | | > 5 × ULN |
| Uric Acid | | |
| (mcmol/L) | | > 713.817 |
| (mg/dL) | | > 12.0 |
| Phosphate | | |
| (mmol/L) | < 0.6 | |
| (mg/dL) | < 2.0 | |
| Calcium, Serum | | |
| (mmol/L) | < 1.75 | > 3.1 |
| (mg/dL) | < 7.0 | > 12.5 |
| Sodium (mmol/L) | < 130 | > 155 |
| Potassium (mmol/L) | < 3.0 | > 6.0 |
| Magnesium | | |
| (mmol/L) | < 0.4 | > 1.23 |
| (mg/dL) | < 0.9 | > 3.0 |
| Glucose | | |
| (mmol/L) | < 2.2 | > 13.9 |
| (mg/dL) | < 40 | > 250 |
| Albumin | | |
| (g/L) | < 20 | |
| (g/dL) | < 2 | |

**Table 11. Criteria for Potentially Clinically Significant Chemistry Values (Continued)**

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

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

### 11.3.2 Statistical Methods

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

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

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

The number and percentage of subjects with post-baseline values during the Treatment Periods meeting the specified criteria for Potentially Clinically Significant (PCS) laboratory values (defined in Table 10 and Table 11) will be summarized for each treatment arm. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A separate listing will be provided that presents all lab values for the subjects meeting PCS criteria during treatment.

For hemoglobin and the liver function tests (LFTs) of alkaline phosphatase, and total bilirubin, the number and percentage of subjects with a maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade of 1, 2, 3, or 4 (see definitions in Table 12) at any post-baseline visit (regardless of the baseline value) through the end of treatment (i.e., Final Treatment Value) will be summarized for each treatment arm. All LFT tables will include summary rows for the number and percentage of subjects with at least Grade 2 and at least Grade 3 laboratory abnormalities. The hemoglobin table will include a summary row for the number and percentage of subjects with at least a Grade 2 laboratory abnormality.

For the liver function tests (LFTs) of ALT and AST, the number and percentage of subjects in with a maximum CTCAE Grade of 1, 2, 3, or 4 (see definitions in Table 12) at any post-nadir visit (regardless of the baseline value) through the end of treatment (i.e., Final Treatment Value) will be summarized for each treatment arm. Note, for these analyses, the nadir is used for reference instead of baseline. Both ALT and AST tables will include summary rows for the number and percentage of subjects with at least Grade 2 and at least Grade 3 laboratory abnormalities.

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

**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 in each treatment arm with maximum on treatment lab values meeting the following criteria will be summarized:

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

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

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

## 11.4 Analysis of Vital Signs and Weight

### 11.4.1 Variables and Criteria Defining Abnormality (if Applicable)

Vital sign variables are body temperature (oral), 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<br>A decrease of ≥ 20 mmHg from baseline | ≥ 180 mmHg AND<br>An increase of ≥ 20 mmHg from baseline |
| Diastolic Blood Pressure | ≤ 50 mmHg AND<br>A decrease of ≥ 15 mmHg from baseline | ≥ 105 mmHg AND<br>An increase of ≥ 15 mmHg from baseline |
| Heart Rate | ≤ 50 bpm AND<br>A decrease of ≥ 15 bpm from baseline | ≥ 120 bpm AND<br>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<br>An increase of ≥ 1.1°C from baseline |

### 11.4.2 Statistical Methods

Vital signs will be summarized at each visit during the Treatment 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 Treatment and Post-Treatment Periods.

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

The number and percentage of subjects with post baseline values during the Treatment Period meeting Criteria for Potentially Clinically Significant Vital Sign Values (Table 13) will be summarized for each treatment arm. 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 SAP

1. Updates were made to the resistance analysis plan to be consistent across the HCV program.

## 12.2 Summary of Changes from SAP Version 1.0

1. Resistance analyses were updated to incorporate the following changes:
    a. Added signature amino acid positions in genotypes 2 – 3.
    b. Resistance analysis will be conducted at 2% instead of 1% detection threshold to reduce reporting of variants considered as "noise."
    c. Updated analyses for each HCV subtype and study arms within each listing.
2. Updated analysis interval of exposure and the definition of EOTR to fit all arms with different treatment duration.
3. Corrected the title of Table 5.
4. Added re-infection to be consistent across the HCV program.

# 13.0 References

1. Szende A, Williams A, editors. Measuring self-reported population health: an international perspective based on EQ-5D-5L. EuroQol Group Monographs Volume 1. SpringMed, 2004.
2. Rabin R, Oemar M, Oppe M, et al. EQ-5D-5L User Guide: Basic Information on How to Use the EQ-5D-5L Instrument, Version 1.0. April 2011.

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