1.0 Title Page

Statistical Analysis Plan

Study M15-828

A Randomized, Open-Label, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults with Genotype 2 Chronic Hepatitis C Virus Infection (CERTAIN-2)

31 October 2016

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the AbbVie Statistics and Statistical Programming Departments for Study M15-828. Study M15-828 assesses the efficacy and safety of 8 weeks of treatment with the combination regimen ABT-493/ABT-530 in chronic HCV genotype 2 (GT2) infected DAA treatment-naïve Japanese adult subjects.

This SAP provides details to further elaborate the statistical methods outlined in the Clinical Study Protocol M15-828 Amendments 1 and 2 including Administrative Change 1 dated 17 June 2016, and describes analysis conventions to guide the statistical programming. Analyses will be performed using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objectives of this study are to assess the efficacy and safety of 8 weeks of treatment with the combination regimen ABT-493/ABT-530 compared to 12 weeks of treatment with SOF and RBV in HCV GT2-infected Japanese adults without cirrhosis.

The secondary objectives are to assess:

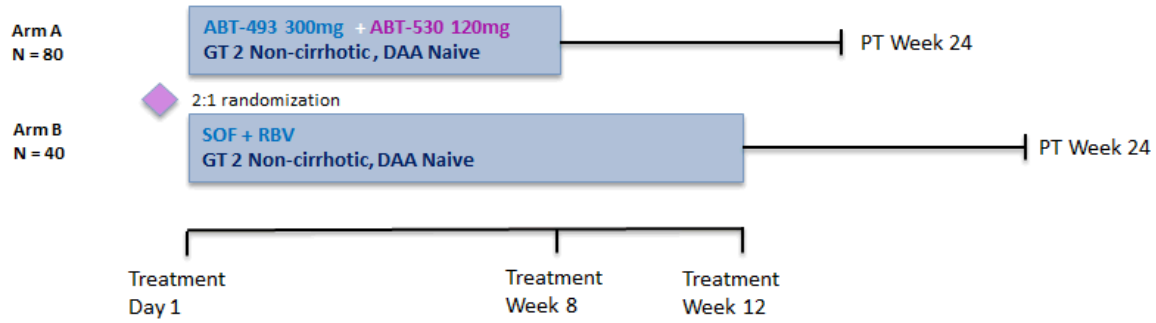
- The percentage of subjects achieving SVR_{12} for Arm A;
- The percentages of subjects with on-treatment virologic failure;
- The percentages of subjects with post-treatment relapse.

Additional objectives are to assess pharmacokinetics and emergence and persistence of viral variants in these treatment regimens.

4.2 Design Diagram

This is a Phase 3, randomized, open-label, active-control, multicenter study to evaluate the efficacy, safety and pharmacokinetics of ABT-493/ABT-530 in chronic HCV GT2-infected HCV DAA treatment-naïve Japanese adult subjects without cirrhosis. This study consists of a Treatment Period (TP) and a Post-Treatment (PT) Period.

Figure 1. Study Schematic



Approximately 120 HCV GT2-infected DAA treatment-naïve subjects (including subjects who are IFN treatment experienced with or without RBV) without cirrhosis will be enrolled into one of two treatment arms (80 subjects into Arm A and 40 subjects into Arm B)

- Arm A: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks;
- Arm B: SOF 400 mg QD plus RBV (600 – 1000 mg based on weight divided BID) for 12 weeks.

Subjects meeting all eligibility criteria will be randomized to Arms A or B. The randomization will be stratified by prior IFN-experience (naïve versus experienced) and screening HCV RNA viral load (< or ≥ 6 million IU/mL). Subjects will be randomized in a 2:1 ratio to Arms A (80 subjects) or B (40 subjects).

4.3 Sample Size

It is planned to enroll a total of 120 subjects in this study. The primary efficacy endpoint of SVR_{12} will be assessed between treatment Arms A and B.

For the primary endpoint, with 80 subjects in the ABT-493/ABT-530 8-week arm (Arm A) and 40 subjects in the SOF plus RBV 12 week arm (Arm B) and assuming that 96% of the subjects in Arm A achieve SVR_{12} and 95% of subjects in Arm B (Table 1) achieve SVR_{12}, this study has > 80% power to demonstrate non-inferiority of the ABT-493/ABT-530 8-week treatment arm compared to the active control in SVR_{12} rate (i.e., a two-sided 95% lower confidence bound for the difference above the non-inferiority margin of –10%). The 10% margin is considered to be an appropriate potential loss of efficacy given the possibility that the current regimen may provide additional clinical advantage over the comparator regimen by shortening the duration of treatment to 8 weeks and eliminating the need for RBV.

Table 1. SVR_{12} Rates in GT2-Infected Non-Cirrhotic Subjects

Trial	SVR (n/N)	SVR (%)
FISSION[1]	59/61	97%
POSITRON[1]	85/92	92%
FUSION[1]	26/29	90%
VALENCE[1]	59/63	94%
Japanese Study[2]	132/136	97%
Total	**361/381**	**95%[a]**

a. The SVR rate is an unweighted average across the studies.

Note: Data included in the table is for 12-week SOF plus RBV regimen across multiple clinical trials in GT2-infected non-cirrhotic subjects.

4.4 Primary Analysis

The primary analysis will occur after all subjects have completed the PT Week 12 Visit or prematurely discontinued the study. The data for the primary analysis will be locked after data cleaning. Results from the primary analysis (e.g., SVR_{12} data) will be described in

the primary clinical study report (CSR) and submitted to regulatory agencies as part of an NDA submission.

The final analysis will be conducted when all subjects enrolled in the study have completed the 24 week post-treatment visit or prematurely discontinued from the study. Data after the primary analysis will be added to a new version of the database which will be cleaned and locked at the end of the study.

4.5 Interim Analysis

An interim analysis that was not specified in the protocol will occur after all subjects have completed the Post-Treatment Week 4 Visit or prematurely discontinued from the study. This interim analysis will include sustained virologic response 4 weeks after end of treatment (SVR_4). The primary endpoint of the study remains unchanged as SVR_{12}. No decision to stop or adjust treatment will be based on this interim analysis and no inference will be performed at the SVR_4 interim analysis so no adjustment of multiplicity will be implemented. The intention is to follow all subjects who receive study drug for 24 weeks following treatment as specified in the protocol. The interim analysis will include analyses of the endpoints specified in the protocol and this SAP for data collected through this time point, except pharmacokinetic and exposure-response analyses, and resistance analyses. This interim analysis will support regulatory submission activities for ABT-493/ABT-530 in Japan.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

5.1.1 Intention-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized subjects who receive at least one dose of study drug. Efficacy analyses will be performed on the ITT population, unless otherwise specified. The data from the ITT population will be presented in efficacy analyses by the treatment arm assigned at the time of randomization.

5.1.2 Modified Intent-to-Treat (mITT) Populations

Sensitivity analyses of the primary efficacy endpoint, when applicable, will be performed on two modified ITT populations below:

Modified ITT Genotype (mITT-GT) Population

mITT-GT population includes subjects in the ITT population excluding subjects with genotype other than HCV GT2 infection as determined in Section 10.9.

Modified ITT Genotype and Virologic Failure (mITT-GT-VF) Population

mITT-GT-VF includes all subjects in the ITT-GT population defined above, excluding subjects who did not achieve SVR_{12} for reasons other than virologic failure.

Demographic analyses will also be performed on the mITT population(s), if needed.

5.1.3 Safety Population

All subjects who receive at least one dose (≥ 1 tablet) of study drug will be included in the safety population. Safety and demographic analyses will be performed on the safety population and presented by the treatment arm assigned.

5.2 Variables Used for Stratification of Randomization

Subjects meeting all eligibility criteria will be randomized to Arm A or B. The randomization will be stratified prior IFN-experience (naïve versus experienced) and screening HCV RNA viral load (< or ≥ 6 million IU/mL). Subjects will be randomized in a 2:1 ratio to Arm A or B.

6.0 Analysis Conventions

6.1 Definition of Baseline and End of Treatment Assessment

6.1.1 Baseline

The baseline value refers to the last available measurement collected before the first dose of study drug is received. The protocol specifies that all Day 1 assessments (other than intensive PK samples) are to be performed prior to administering the first dose of study drug. Therefore, all Day 1 assessments for which time is not collected will be assumed to be pre-dose and the baseline value will be the last available measurement collected on or before the first day of study drug administration. All Day 1 assessments with time available must be before the time of first dose to be considered baseline and the last available measurement collected before the date and time of the first dose of study drug will be considered the baseline value. If multiple measurements that are prior to dosing are recorded on the same date and with the same time or if time is not available, then the average of these measurements will be considered the baseline value. The same baseline value will be used for analyses of the Treatment and Post-Treatment Periods.

Safety laboratory assessments that are related to a serious adverse event that occurred on the first dose day will not be used as baseline values.

6.1.2 Study Days

Study days 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 date the first study drug is taken. Study days are positive values when the time point of interest is after the date the first study drug dose is taken. There is no Study Day 0. Study Day 1 is the day the first dose of study drug is taken.

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

Study drug end days are calculated for each time point relative to the date the last dose of study drug is taken. The last day of study drug dosing 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 is defined as the last available 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 available measurement collected after Study Drug End Day 2 and on or before Study Drug End Day 999.

6.2 Definition of Analysis Windows

For analyses of HCV RNA and resistance, the time windows specified in Table 2 and Table 3 describe how efficacy data are assigned to protocol-specified time points during the Treatment and PT Periods, respectively. All time points and corresponding time windows are defined based on the date/time of blood sample collection.

For laboratory data and vital signs, the time windows specified in Table 2 and Table 4 describe how data are assigned to protocol specified time points during the Treatment and Post-Treatment periods respectively.

If more than one assessment is available for a time window, the assessment closest (except in analyses of SVR) to the nominal time will be used. If there are two observations equally distant to the nominal time, the latest one will be used in analyses. For analyses of SVR (e.g., SVR_{12}), 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 to calculate descriptive statistics and in analyses of the mean change from baseline.

Table 2. Analysis Time Windows for HCV RNA, Resistance Endpoints, Laboratory, Vital Sign Measurements, and PRO Instruments (Treatment Period)

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Day 1/Baseline[a]	1	≤ 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
Week 12[b]	84	71 to 98
Final Treatment Visit[c]	2 to ≤ 2 days after last dose of study drug	

a. Day of first dose of study drug.

b. For 12-week treatment only.

c. 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. PRO instruments are collected at Day 1 and End of Treatment Visit, which can be at Weeks 8 or 12 depending on treatment assignment.

Table 3. Analysis Time Windows for HCV RNA and Resistance Endpoints (Post-Treatment Period)

Scheduled Visit[a]	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Day Range)
Post-Treatment Week 2	14	3 to 21
Post-Treatment Week 4	28	22 to 42
Post-Treatment Week 8	56	43 to 70
Post-Treatment Week 12	84	71 to 126
Post-Treatment Week 24	168	127 to 999
SVR_4[b]	28	3 to 56
SVR_{12}[b]	84	57 to 126
SVR_{24}[b]	168	127 to 210

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

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

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

Table 4. Laboratory Data, Vital Sign and PRO Instruments 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 70
Post-Treatment Week 12	84	71 to 126
Post-Treatment Week 24	168	127 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 PT visit; hematology, chemistry, urinalysis, and coagulation panels are collected only at PTW4 or PTDC (if subject discontinued prior to PTW4). PRO instruments are collected at PTW12 only.

6.3 Missing Data Imputation

Missing Data Imputation for SVR

HCV RNA values will be selected for analysis based on the analysis windows defined in Section 6.2. HCV RNA values from central laboratory will be used as described in Section 10.1, unless otherwise specified.

For analyses of SVR, subjects missing a visit HCV RNA value will have backward imputation applied, if possible. For backward imputation, if the nearest HCV RNA value after the SVR window is unquantifiable or undetectable, then it will be used to impute the HCV RNA value in the SVR window. If a subject continues to be missing an HCV RNA value within the appropriate SVR window after performing backward imputation, then this value will be imputed using an HCV RNA value from a local laboratory if available; otherwise, the HCV RNA value for that window will be considered missing. Subjects with missing HCV RNA data in the analysis window, after applying these imputations, will be imputed as a failure of viral response.

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

Missing Data Imputation for Virologic Failure

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

Missing Data Imputation for PRO Questionnaires

For EQ-5D-3L index and VAS scores, no imputation will be performed for missing items. 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.

If a subject starts another treatment for HCV, then all PRO values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses.

No imputation will be performed for missing data in other than specified above.

7.0 Demographics, Baseline Characteristics, Medical History, and Other Medications

The safety population will be used to summarize demographics and baseline characteristics, medical history and previous, concomitant, and post-treatment medications for each treatment arm.

7.1 Demographic and Baseline Characteristics

Categorical demographic and baseline characteristic variables will be summarized with the number and percentage of subjects in each category and proportions will be compared across treatment arms with a chi-square test. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, maximum and minimum), and means will be compared across the treatment arms with a one-way analysis of variance (ANOVA).

Continuous demographic variables include age, weight, height, waist circumference, and body mass index (BMI). Categorical demographic variables include sex, race, ethnicity, age category (< 65 years, $\geq 65 - < 75$ years, ≥ 75 years), and BMI category (< 25 or ≥ 25 kg/m^2).

Continuous baseline characteristics include baseline $\log_{10}$ HCV RNA level, homeostasis model of assessment – insulin resistance (HOMA-IR), creatinine clearance, eGFR, platelet count, albumin, GGT, LDL, HDL, APRI, FIB-4, AST, ALT, total, direct, and indirect bilirubin for all subjects.

Categorical baseline characteristics include:

- HCV genotype 2 subtype (as determined by the central laboratory);
- HCV genotype 2 subtype (as determined by phylogenetic analysis);
- Prior HCV treatment history (naïve or experienced);
- For treatment experienced subjects, type of non-response to previous treatment (non-responder, breakthrough, relapse, or unknown/other);
- IL28B genotype (CC, CT, or TT; CC or non-CC);
- Baseline HCV RNA level (< 100,000 IU/mL or ≥ 100,000 IU/mL; < 800,000 IU/mL or ≥ 800,000 IU/mL; < 6,000,000 or ≥ 6,000,000 IU/mL; < 10,000,000 IU/mL, or ≥ 10,000,000 IU/mL);
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, F4 (if applicable));
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L; < 150 or ≥ 150 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, ≥ 90 mL/min);
- Baseline eGFR (< 30, ≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73 m^2);
- Baseline HOMA-IR (< 2 or ≥ 2 mU × mmol/L^2) and (< 3 or ≥ 3 mU × mmol/L^2);
- History of diabetes (yes/no);
- History of bleeding disorders (yes/no);
- History of depression or bipolar disorder (yes/no);
- History of cardiovascular disease (yes/no);
- Baseline metabolic syndrome (yes/no);
- Injection drug use (yes, within last 12 months; yes, more than 12 months ago; or no);

- Tobacco use (user, ex-user, or non-user);
- Alcohol use (drinker, ex-drinker, or non-drinker);
- Concomitant use of Proton Pump Inhibitors (PPIs);
- Concomitant treatment with liver protectants (yes/no);
- Concomitant use of Calcium Channel Blockers (CCBs) (yes/no)
- Subject with high risk of carcinogenesis (Yes/No) per JSH guidance;[3]
- Subject with advanced fibrosis (Yes/No) per JSH guidance.[3]

Summaries of baseline resistance analyses are described in Section 10.9.

Any concomitant medication coded to the WHO Drug Dictionary ATC code of A02BC will be counted as a PPI.

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

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 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 available 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 5.

A subject is categorized as high risk of carcinogenesis if fibrosis stage score ≥ F3 or platelet count < 120 × 10^9/L with age ≥ 66 years. A subject is categorized as advanced fibrosis if fibrosis stage score ≥ F2 or platelet count < 150 × 10^9/L with age ≥ 66 years.

All subjects will be categorized as not having cirrhosis (cirrhosis = no) since this study excludes subjects with cirrhosis.

Table 5. Baseline Fibrosis Stage

Baseline Fibrosis Stage, Metavir Equivalents	Liver Biopsy Metavir, Batts Ludwig, Knodell, IASL, Scheuer, Laennec Score, or New Inuyama 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

* APRI will not be used to derive Baseline Fibrosis Stage. However, per inclusion/exclusion criteria, subjects need to have concordant FibroTest and APRI scores in order to determine eligibility.

Baseline APRI and FIB-4 are defined as the equations below. Subjects who do not have concurrent AST and platelet values at baseline will be excluded from the summary of baseline APRI. Age is defined in years at baseline. Subjects who do not have concurrent values of AST, ALT, and platelet count at baseline, or subjects who are missing age will be excluded from the summary of FIB-4.

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

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

Subjects will be classified as having metabolic syndrome if at least 3 of the 5 characteristics in Table 6 are present.

Table 6. Clinical Identification of Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference	
Men	> 102 cm (> 40 in)
Women	> 88 cm (> 35 in)
Triglycerides	≥ 150 mg/dL
HDL cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure[a]	≥ 130/≥ 85 mmHg
Fasting glucose	≥ 100 mg/dL

a. Raised blood pressure defined as either systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg.

Reference: Grundy 2004.[4]

Histories of diabetes, bleeding disorders, depression or bipolar disorder, and cardiovascular disease will be based on the Medical History (MH) eCRF, as defined in Table 7.

Table 7. Medical History eCRF

	Medical History eCRF	
Subgroup	**Body System**	**Condition/Diagnosis**
Diabetes	Metabolic	Diabetes mellitus
Bleeding disorders	Blood	Clotting/bleeding problems
		Factor deficiency
		Hemophilia
		Von Willebrand disease
Depression or bipolar disorder	Neurologic and Psychiatric System	Bipolar disorder
		Depression
Cardiovascular disease	Cardiovascular	Angina
		Cardiac arrhythmia
		Cardiovascular disease
		Congenital heart disease
		Congestive heart failure
		Coronary artery disease
		Hypertension
		Myocardial infarction
		Myocarditis
		Peripheral vascular disease-arterial
		Peripheral vascular disease-venous
		Valvular heart disease
		Vasculitis

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized 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 Prior, Concomitant and Post-Treatment Medications

A prior medication is defined as any medication taken prior to the date of the first dose of study drug (ABT-493/ABT-530 or SOF + RBV). A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken on or after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug. A post-treatment medication for the treatment of HCV is defined as any medication taken on or after the last dose of study drug and entered as "Post-treatment HCV medications" on the eCRF.

The number and percentage of subjects taking prior medications, concomitant medications, and post-treatment HCV medications will be summarized for each treatment arm by generic drug name based on the WHO Drug Dictionary. Prior medications will be divided by the following categories:

- The prior anti-HCV medications taken by treatment experienced subjects;
- All other prior medications for all treated subjects.

8.0 Patient Disposition

The number and percentage of subjects who screen failed for any reason, and for each screen failure reason, will be summarized for all subjects who screen failed.

8.1 Disposition of Safety Population

The number of subjects in 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 prematurely discontinued study drug;
- Subjects who completed the study;
- Subjects who prematurely discontinued from the study;
- Subjects ongoing in the Post-Treatment Period at the time of the primary analysis.

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

The number and percentage of subjects with reported study drug interruptions will be summarized by treatment arm.

Reasons for study drug interruptions 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 for 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 and for the study total.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for exposure during the treatment period.

Study drug duration 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 ≥ 52 days for Arm A and ≥ 77 days for Arm B will be summarized.

9.2 Compliance

At each visit (starting with the Week 4 visit) during the Treatment Period, the total number of tablets dispensed and returned is recorded. The compliance for study drug (ABT-493/ABT-530, SOF, and RBV) during the treatment period will be calculated as the percentage of tablets taken relative to the total tablets expected to be taken. The total number of tablets expected to be taken 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 of study drug – date of first dose of study drug + 1). Study drug interruptions recorded on the eCRF will not be subtracted from the duration. For compliance to RBV, RBV dose modifications due to adverse events, toxicity management, or weight changes as recorded on the RBV Dose Modifications eCRF will be used to modify the total number of tablets that should have been taken.

A subject is considered to be compliant to each study drug if the percentage of compliance for that type is between 80% and 120%. Compliance will be calculated for each subject and each tablet type by treatment arm and summarized with the mean, median, standard deviation, minimum, and maximum. The percentage of compliant subjects will be summarized for each study drug and each treatment arm, based on data as observed. An additional summary of the percentage of compliant subjects will be provided where subjects who are missing study drug accountability records will be imputed as non-compliant.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

Treatment effects will be evaluated based on a 2-sided significance level of 0.050 (when rounded to three decimal places), and all efficacy analyses will be performed on the ITT population, unless otherwise specified.

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

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for this assay (regardless of genotype) are both 15 IU/mL.

HCV RNA results that are detectable but not quantifiable are reported as "< 15 IU/ML HCV RNA DETECTED" and those that are undetectable are reported as "HCV RNA NOT DETECTED" in the database.

The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 15 IU/mL, including values reported as "HCV RNA NOT DETECTED" or "< 15 IU/ML HCV RNA DETECTED." HCV RNA ≥ LLOQ are all quantifiable values.

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

Definitions for Efficacy Endpoints

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

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

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

On-treatment virologic failure = Breakthrough or EOT failure.

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.

$Relapse_4$ = confirmed HCV RNA ≥ LLOQ between end of treatment and 4 weeks after last actual dose of study drug (up to and including the SVR_4 assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment (defined as study drug duration ≥ 52 days for Arm A and ≥ 77 days for Arm B), excluding reinfection as described below.

$Relapse_{12}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR_{12} assessment time point) for a

subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment (defined as study drug duration ≥ 52 days for Arm A and ≥ 77 days for Arm B), excluding reinfection as described below.

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

Relapse$_{overall}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the PT Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment (defined as study drug duration ≥ 52 days for Arm A and ≥ 77 days for Arm B), excluding reinfection.

Only subjects who have at least one post-treatment HCV RNA value will be included in analyses of relapse. For the analysis of relapse, completion of treatment is defined as any subject with study drug duration of 52 days or greater for Arm A and 77 days or greater for Arm B. If the last available post-treatment value is ≥ LLOQ, then the subject will be considered a relapse (i.e., will not require confirmation).

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

Post-treatment relapse is defined as described earlier (**Relapse$_{12}$, Relapse$_{24}$, Relapse$_{overall}$**), and no genotype, subtype, or clade switch compared with baseline as

determined by phylogenetic analysis of the NS3 or NS5A gene sequences. If phylogenetic analysis is not possible due to technical difficulties, the subject will be defined as having a post-treatment relapse unless an HCV genotype or subgenotype switch is confirmed by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Reasons for SVR_4 Non-Response

Subjects who do not achieve SVR_4 (SVR_4 non-responders) will be categorized as having:

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. Relapse by Post-Treatment Week 4 (defined according to the **$Relapse_4$** 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 [study drug duration < 52 days for subjects in Arm A, and < 77 days for subjects in Arm B] and did not meet the **On-treatment virologic** failure definition);
4. HCV reinfection (see definition described earlier);
5. Missing follow-up data in the SVR_4 window (defined as any subject who completed study drug without data in the SVR_4 window after applying the imputation rules and not meeting the definitions of [1], [2], [3], or [4]);
6. Other (defined as any SVR_4 non-responder not meeting the definitions of [1] – [5]).

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 [study drug duration < 52 days for subjects in Arm A, and < 77 days for subjects in Arm B] and did not meet the **On-treatment virologic** failure definition);
4. HCV reinfection (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 after applying the imputation rules 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]).

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$_{24}$** definition);
4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{24} non-responder who prematurely discontinued study drug [study drug duration < 52 days for subjects in Arm A, and < 77 days for subjects in Arm B] and did not meet the **On-treatment virologic failure**, **Relapse$_{12}$**, or **Relapse$_{24}$** definitions);
5. HCV reinfection;

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

10.2 Handling of Multiplicity

No adjustment for multiple comparisons is used.

10.3 Primary Efficacy Analysis

The primary efficacy variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

The primary efficacy endpoint is:

- Non-inferiority of the ABT-493/ABT-530 8-week regimen (Arm A) to the SOF and RBV 12 week regimen (Arm B) in SVR_{12} using a non-inferiority margin of 10% in the ITT population.

For the primary efficacy endpoint, to show non-inferiority of the SVR_{12} rate of the ABT-493/ABT-530 8-week regimen (Arm A) to that of the SOF and RBV 12-week regimen (Arm B), the percentage of subjects achieving SVR_{12} will be calculated for each arm and a two-sided 95% confidence interval for the difference in SVR_{12} rates (Arm A minus Arm B) will be calculated using the normal approximation to the binomial distribution, unless the SVR_{12} rates are 100% for both Arm A and Arm B, then the Wilson's score method will be used for the confidence interval instead. All subjects in the ITT population will be used when calculating SVR_{12}. If the lower bound of the confidence interval for the difference is above the non-inferiority margin of –10%, then the ABT-493/ABT-530 8-week regimen will be considered non-inferior to SOF and RBV 12 week regimen.

10.4 Interim Analysis

The efficacy variable for the interim analysis is SVR_4 (HCV RNA < LLOQ 4 weeks after the last actual dose of study drug).

The interim efficacy endpoint analysis is:

- The difference between the ABT-493/ABT-530 8-week regimen (Arm A) to the SOF and RBV 12 week regimen (Arm B) in SVR_4.

For the interim analysis, the difference between the SVR_4 rate of Arm A and that of the Arm B will be calculated along with a two-sided 95% confidence interval for the difference in SVR_4 rates (Arm A minus Arm B) using the normal approximation to the binomial distribution, unless the SVR_4 rates are 100% for both Arm A and Arm B, then the Wilson's score method will be used for the confidence interval instead. All subjects in the ITT population will be used when calculating SVR_4 rates.

10.5 Secondary Efficacy Analyses

The following secondary endpoints will be summarized:

- the percentage of subjects achieving SVR_{12} for Arm A (the ABT-493/ABT-530 8-week regimen)
- the percentage of subjects in each treatment arm with on-treatment virologic failure (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and
- the percentage of subjects in each treatment arm with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment, excluding subjects who have been shown to be reinfected).

For the first secondary efficacy endpoint, the percentage of achieving SVR_{12} in Arm A and a two-sided 95% confidence interval will be calculated using the normal approximation to the binomial distribution, unless the rate is 100% and then the Wilson's score method will be used.

The percentage of subjects with on-treatment virologic failure and post-treatment relapse will be summarized for each treatment arm. Two-sided 95% confidence intervals will be provided for rates within treatment arms and for the difference between arms (Arm A minus Arm B) using Wilson's score confidence intervals. For the analysis of relapse and reinfection, completion of treatment is defined as any subject assigned to the12-week treatment with study drug duration of 77 days or greater; or any subject assigned to the 8-week treatment with study drug duration of 52 days or greater. Subjects with probable reinfection based on HCV sequencing or differing post-treatment HCV genotype or subtype will be summarized separately from relapse.

In addition, a summary of reason for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, re-infection, other) will be provided for each treatment arm.

Similar secondary endpoint analyses (SVR_4 in Arm A, on-treatment virologic failure in each arm, and relapse through PT Week 4) will be performed for the interim analysis.

10.6 Sensitivity Analyses for SVR

The following analysis approaches will be used as sensitivity analyses for evaluating SVR_{12} rates within and between treatment arms for the primary efficacy endpoint:

- A two-sided 95% confidence interval for the SVR_{12} rates within each arm will be calculated using a Wilson score interval.
- The percentage of subjects achieving SVR_{12} will be compared using a logistic regression model with treatment arm as a factor, and baseline $\log_{10}$ HCV RNA level, HCV genotype 2 subtype, and prior HCV treatment history as coviariates.

- The difference in SVR_{12} rates (Arm A minus Arm B) will be analyzed using a stratum-adjusted Mantel-Haenszel (MH) proportion with a continuity correction for variance, adjusting for both of the randomization stratum (described in Section 5.2).
- A two-sided 95% confidence interval for the difference in SVR_{12} rates (Arm A minus Arm B) will be calculated using a Wilson score interval.

The above analyses will be performed on the ITT, and mITT-GT-VF populations, as applicable. The same sensitivity analyses will be performed for SVR_4 in the interim analysis.

10.6.1 Imputation Approaches

In addition to imputing SVR_{12} as described in Section 6.3, SVR_{12} rates will be calculated using the following other methods to impute missing HCV RNA values:

- imputing any missing HCV RNA values in the SVR_{12} window by carrying forward the last non-missing (post-baseline) HCV RNA value prior to the SVR_{12} window;
- impute as described in Section 6.3 but treat SVR_{12} non-responders who were categorized as "prematurely discontinued study drug with no on-treatment virologic failure" or "missing follow-up data in the SVR_{12} window" as successes.

For each of these, the percentage of subjects with SVR_{12} in each arm and the difference between arms will be presented along with two-sided 95% confidence intervals. The same sensitivity analyses will be performed for SVR_4 in the interim analysis.

10.6.2 Assessment of Homogeneity Across Stratification Variables

Heterogeneity across the randomization stratification variable will be examined for the primary efficacy endpoint of SVR_{12} using the chi-square test of homogeneity. The four strata for the ITT population are:

1. IFN-Naïve, Screening HCV RNA < 6 million IU/mL;
2. IFN-Naïve, Screening HCV RNA ≥ 6 million IU/mL;
3. IFN-Exp, Screening HCV RNA < 6 million IU/mL;
4. IFN-Exp, Screening HCV RNA ≥ 6 million IU/mL.

The proportion of subjects in each treatment arm with SVR_{12} will be calculated across strata using stratum weighted proportions.

p_s = the proportion of subjects with SVR_{12} among *N* subjects, which can be defined as:

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

where N represents the number of subjects in each arm within the ITT population, p_h = the proportion of subjects achieving SVR_{12} in stratum *h,* N_h represents the number of subjects in stratum *h,* $W_h = N_h/N$, and $N = \sum_{h=1}^{H} N_h$..

Accompanying confidence intervals based on stratum-weighted variances will be calculated using the equations below. The variance of p_s will be estimated by:

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

and the 2-sided 95% confidence interval will be calculated as $p_s \pm z$, $\sqrt{Var(p_s)}$ where z is the 1-α/2 point of the standard normal distribution.

In addition, the number and percentage (p_h) of subjects achieving SVR_{12} within each of the four strata will be presented.

The difference in SVR_{12} rates between Arm A and Arm B in h*th* stratum will be calculated as $d_h = p_{1h} - p_{2h}$. The variances for the difference in proportions, d_h, within the h*th* stratum will be calculated using the simple asymptotic methods, $Var(d_h) =$

$p_h^* q_h^* (1/n_{1h} + 1/n_{2h})$ where $p_h^* = (n_{1h}p_{1h} + n_{2h}p_{2h})/(n_{1h} + n_{2h})$ and $q_h^* = 1 - p_h^*$, and the 2-sided 95% confidence interval will be calculated as $d_h \pm z\sqrt{Var(d_h)}$, where z is the 1 – α /2 point of the standard normal distribution. The differences in SVR_{12} rates and accompanying CI will be presented for each strata.

Differences in proportions between Arm A and Arm B across strata will be calculated based on stratum-adjusted Mantel-Haenszel (MH) proportions, where the difference in the proportions is calculated as $d = \sum_{h=1}^{H} w_h d_h / \sum_{h=1}^{H} w_h$ where $d_h = p_{1h} - p_{2h}$ is the difference in the proportions between Arm A and Arm B in hth stratum and $w_h = (n_{1h}n_{2h})/(n_{1h} + n_{2h})$ is the weight for hth stratum. Its continuity corrected variance will be estimated by:

$$Var(d) = \frac{\sum_{h=1}^{H} w_h^2 \left(\frac{p_{1h}^*(1 - p_{1h}^*)}{n_{1h} - 1} + \frac{p_{2h}^*(1 - p_{2h}^*)}{n_{2h} - 1}\right)}{\left(\sum_{h=1}^{H} w_h\right)^2}$$

Where $p_{1h}^* = (m_{1h} + 0.5)/(n_{1h} + 1)$ and $p_{2h}^* = (m_{2h} + 0.5)/(n_{2h} + 1)$ with $m_{1h} = n_{1h}p_{1h}$ and $m_{2h} = n_{2h}p_{2h}$. So the 2-sided 95% confidence interval will be calculated as $d \pm z\sqrt{Var(d)}$ where z is the 1 – α/2 point of the standard normal distribution.

The same assessment of heterogeneity across strata will be performed for SVR_4 in the interim analysis.

10.7 Efficacy Subgroup Analysis

Subgroup analyses will be performed for the primary efficacy endpoint of SVR_{12}.

Within each subgroup, the percentage of subjects with SVR_{12} within each arm and the difference between treatment arms in the percentage of subjects with SVR_{12} will be calculated, as will the corresponding two-sided 95% Wilson score intervals. A test of homogeneity will be conducted (Zelen's exact test) to evaluate whether differences between treatment arms are consistent across subgroups (i.e., confidence intervals for the difference in SVR_{12} rates will not be compared to the non-inferiority margin).

Tests will be conducted at the nominal 0.05 level. The 2-sided 95% Wilson score confidence interval will be produced if there are at least 10 subjects in the subgroup.

The following subgroups will be analyzed:

- HCV genotype 2 subtype (final subtype as defined in Section 10.9);
- Prior HCV treatment history (naïve or IFN-experienced);
- IL28B genotype (CC or non-CC);
- Sex (male or female);
- Age (< 65 years, ≥ 65 – < 75 years, ≥ 75 years);
- BMI (< 25, or ≥ 25 kg/m^2);
- Baseline HCV RNA level (< 100,000 IU/mL or ≥ 100,000 IU/mL; < 800,000 IU/mL or ≥ 800,000 IU/mL; < 6,000,000 or ≥ 6,000,000 IU/mL; < 10,000,000 IU/mL, or ≥ 10,000,000 IU/mL);
- Baseline fibrosis stage (F0 – F1, F2, F3, F4 (if applicable));
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L; < 150 or ≥ 150 × 10^9/L);
- Baseline HOMA-IR (< 2 or ≥ 2 mU × mmol/L^2) and (< 3 or ≥ 3 mU × mmol/L^2);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, ≥ 90 mL/min);
- Baseline eGFR (< 30, ≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73 m^2);
- History of diabetes (yes/no);
- History of bleeding disorders (yes/no);
- History of depression or bipolar disorder (yes/no);
- History of cardiovascular disease (yes/no);
- Baseline metabolic syndrome (yes/no);
- Injection drug use (yes, within last 12 months; yes, more than 12 months ago; or no);
- Presence of baseline resistance-associated variants (any NS3 variant [yes/no]; any NS5A variant [yes/no]; any NS3 and any NS5A [yes/no], any NS3 or any NS5A [yes/no]) and (NS3 only, NS5A only, both NS3 and NS5A, or none);

- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no);
- DAA compliance (yes/no);
- Concomitant treatment with liver protectants (yes/no);
- Subject with high risk of carcinogenesis (Yes/No);
- Subject with advanced fibrosis (Yes/No).

Subgroup analysis will also be performed on relevant combinations of subgroup variables if deemed clinically meaningful.

For the subgroup analyses, the presence of baseline resistance-associated variants as listed above are defined in Section 10.9.1.

All subgroup analyses will be performed for SVR_4 in the interim analysis except

- Presence of baseline resistance-associated variants (any NS3 variant [yes/no]; any NS5A variant [yes/no]; any NS3 and any NS5A [yes/no], any NS3 or any NS5A [yes/no]) and (NS3 only, NS5A only, both NS3 and NS5A, or none).

A logistic regression model will be used to explore the associations between each of the subgroup variables and SVR_{12} by fitting a logistic regression model on all subjects in the mITT-GT-VF population. Among all candidate predictors, continuous measurements will be used where possible (e.g., continuous baseline $\log_{10}$ HCV RNA level) in the logistic regression model. For the variables on presence of baseline resistance-associated variants, only one unique variable (NS3 only vs. NS5A only vs. both NS3 and NS5A vs. none) will be used in the logistic regression model. A stepwise logistic regression approach will be used to assess the strength of each subgroup variable in predicting SVR_{12}, with a significance level of 0.10 to enter and remain in the model.

10.8 Additional Efficacy Analyses

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

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects with SVR_{24};
- The percentage of subjects with SVR_4 in Arm B;
- The reasons for not achieving SVR_{12} and the reasons for not achieving SVR_{24}
- The percentage of subjects with virologic failure through Post-Treatment Week 4 (i.e., the SVR_4 non-responders due to on-treatment virologic failure or $Relapse_4$).
- The percentage of subjects with virologic failure through Post-Treatment Week 12 (i.e., the SVR_{12} non-responders due to on-treatment virologic failure or $Relapse_{12}$).

In the above analyses for SVR and relapse, the percentage of subjects in each treatment arm with a two-sided 95% Wilson score interval and the (unadjusted) difference in rates (Arm A minus Arm B) with a two-sided 95% Wilson score interval will be summarized. Imputations for missing data will be performed as described in Section 6.3 for analyses of SVR and virologic failure, 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.

A summary of the subjects who completed treatment and relapsed (defined as **$Relapse_{overall}$**) will be prepared displaying the number of subjects relapsing overall and by SVR visit window (within the SVR_4, SVR_{12}, SVR_{24} windows or after SVR_{24} window), including the subject numbers and the SVR visit window corresponding to the first occurrence of relapse. A similar summary and listing will be prepared for subjects who prematurely discontinued treatment and relapsed after having HCV RNA < LLOQ at their Final Treatment Visit.

The number and percentage of subjects who do not achieve SVR_{12} will be summarized by reason for non-response (as defined in Section 10.1). A listing of subject numbers and reason for non-response will be prepared. A similar summary and listing will be prepared for subjects who do not achieve SVR_4 and SVR_{24}.

The concordance between SVR_{12} and SVR_{24} will be assessed for each treatment arm by the agreement between SVR_{12} and SVR_{24} and 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 where both SVR_{12} and SVR_{24} are not achieved. 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_{12} out of all subjects who did not achieve SVR_{12}. Similarly, the concordance between SVR_4 and SVR_{12} will be summarized.

10.9 Resistance Analyses

For all subjects in Arm A, full length NS3/4A or NS5A from baseline samples will be sequenced by next generation sequencing (NGS). Subjects in Arm B will have full length NS5B NGS performed on baseline samples only if they do not achieve SVR_{12}.

Subjects who do not achieve SVR_{12} will have post-baseline resistance testing conducted if (1) they have on-treatment breakthrough; (2) if they have post-treatment relapse, with a study drug duration ≥ 77 days for subjects assigned to 12 weeks of treatment (Arm B) or study drug duration ≥ 52 days for subjects assigned to 8 weeks of treatment (Arm A); or (3) if they have HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment. 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 treatment arm, HCV subtype, prior HCV treatment experience, reason for SVR_{12} 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. All listings described below will also display treatment arm, HCV subtype, prior HCV treatment experience, and reason for SVR_{12} 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 drug who do not achieve SVR_{12} and 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 and the corresponding baseline sample sequenced. For subjects who are lost to follow-up with less than 6 weeks of therapy while not virally suppressed (e.g., HCV RNA never < LLOQ or have increase in viral load post nadir), the sample at the latest available time point with HCV RNA ≥ 1000 IU/mL will be sequenced. These subjects will be referred to as the non-PVF population. A listing of all subjects in the non-PVF population with post-baseline sequencing available will be created that is similar to the listing of subjects in the PVF population with post baseline sequencing available.

For all subjects in Arm A, the region encoding full length NS3/4A and NS5A from their available baseline samples will be sequenced by next generation sequencing (NGS). For subjects in Arm A who do not achieve SVR_{12}, the region encoding full length NS3/4A and NS5A from their virologic failure/early discontinuation samples will be sequenced by NGS. For subjects in Arm B who do not achieve SVR_{12}, the region encoding full length NS5B from their baseline sample and the sample closest in time after VF with an HCV RNA level of ≥ 1000 IU/mL will be sequenced by NGS.

For each DAA target, signature amino acid positions in genotype 2 are listed in Table 8.

Table 8. List of Genotype-Specific Signature Amino Acid Positions and Associated Specific Variants

GT2 Target	Signature Amino Acid Positions	Amino Acid Positions for Subgroup Variant Analysis
NS3/4A	36, 43, 54, 55, 56, 80, 155, 156, 168	155, 156, 168
NS5A	24, 28, 29, 30, 31, 32, 58, 92, 93	24, 28, 30, 92, 93
NS5B	159, 282	

An appropriate subtype specific prototypic reference sequence will be used for comparison with sequences from samples.

The following definitions will be used in the resistance analyses:

- Baseline variant: a variant present by NGS in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on variant frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target.
- 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.
- Post-baseline variant: an amino acid variant in a post-baseline time point sample that was not detected at baseline (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the sample.
- Enriched variant: a variant present at both baseline and in a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20].
- Treatment-emergent variant: A post-baseline variant or an enriched variant.
- Variants emerging at an amino acid position: amino acid position where 2 or more subjects of the same HCV subtype have treatment emergent variants (with all variants at that position listed after the position).

  Emerged variant: a treatment-emergent variant that is observed in 2 or more subjects of the same HCV subtype.

The following (Analyses 1, 2, and 3) will be available in the primary CSR:

Analysis 1: The following analyses will be performed for the arm described:

- The number and percentage of subjects in Arm A with baseline variants at detection-thresholds of 2% and 15% for variants at signature amino acid positions, and 15% for variants at non-signature positions. For analysis by signature amino acid positions, the number of subjects with variants at signature amino acid positions in NS3 only, NS5A only, NS3 + NS5A, any in NS3, any in NS5A, or any in [NS3 or NS5A] will also be provided.

- A listing of all baseline variants (2% detection threshold) at signature amino acid positions for each DAA target (NS3/4A and NS5A) for the ITT population of subjects in Arm A.
- A listing of all baseline variants (15% detection threshold) at non-signature amino acid positions for each DAA target (NS3/4A and NS5A) for the PVF population of subjects in Arm A.
- For subjects in Arm B who experience VF, a listing by subject of all baseline variants relative to prototypic reference sequence will be provided for NS5B.

Analysis 2: The impact of baseline variants on treatment outcome will be assessed for subjects in Arm A in the mITT-GT_VF population 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. Analyses will be grouped by subject's HCV subtype and DAA target (NS3 or NS5A). Subjects not achieving SVR_{12} due to non-virologic reasons will be excluded. These analyses will be performed for the following subgroups based on variants in NS3/4A and NS5A separately:

- Variants at signature amino acid positions (vs. no variant at that position), using detection thresholds of both 2% and 15%. The analysis will also summarize the number of subjects with variants in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A.
- Variants at each non-signature amino acid position (vs. no variant at that position), at a detection threshold of 15%.
- Each variant at a signature amino acid position (vs. not that variant) using detection thresholds of 2% and 15%. The analysis will also summarize the number of subjects with variants in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A.

Analysis 3: The following will be provided for subjects who do not achieve SVR_{12} who have post-baseline resistance data available.

- Listings by subject of all treatment-emergent variants relative to the baseline amino acid sequence will be provided for each DAA target (NS3 and NS5A), separate listings for the PVF and non-PVF populations for subjects in Arm A.
- Listings by subject of all variants at signature amino acid positions in a post-baseline time point for each DAA target (NS3 and NS5A); with separate listings for those in the PVF and non-PVF populations for subjects in Arm A.
- Number and percentage of subjects in Arm A (with listing of subject numbers) with *variants emerging at an amino acid position*, with separate summaries for those in the PVF and non-PVF populations.
- Number and percentage of subjects in Arm A (with listing of subject numbers) with *emerged variants*, with separate summaries for those in the PVF and non-PVF populations.
- For subjects in Arm B who experience virologic failure who have post-baseline resistance data available, a listing by subject of all treatment-emergent variants relative to the baseline amino acid sequence will be provided for NS5B.

The following data will be available in the final CSR:

- Analysis 3 will be updated to include subjects who experience VF after Post-Treatment Week 12.
- The persistence of post-baseline variants at signature amino acid positions for each target (NS3 and NS5A) from subjects in Arm A who fail to achieve SVR_{12} will be assessed at Post-Treatment Week 24. Listings by subject and time point of all treatment-emergent variants will be provided for each DAA target (NS3 and NS5A), separate listings for the PVF and non-PVF populations.

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV sequences from baseline samples from all subjects in order to accurately determine subtype.

Subjects' HCV genotype and subtype may be assessed based on the Inno-LiPA 2.0 Assay used by the Central lab (Covance), the HCV genotype determination by Sanger

sequencing of a region of NS5B by the Central lab (Covance) and/or from phylogenetic analysis of the full length NS3/4A and/or NS5A sequences performed by AbbVie. If the phylogenetic analysis is available, then it will be used to determine the subject's HCV genotype and subtype. If it is not available, then the Sanger sequencing assay result will be used to determine the subject's HCV genotype and subtype, if available. Finally, if neither the phylogenetic analysis result nor the Sanger sequencing assay results are available, then the Inno-LIPA assay results will be used to categorize the subject.

The above algorithm will be used to derive the final subtype used in summaries of efficacy subgroup analyses and resistance analyses.

The baseline characteristic summary will use the results from the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]).

A summary of HCV genotype and subtype as provided by the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]) versus phylogenetic analysis also will be provided.

10.9.1 Presence of Baseline Resistance-Associated Variants

For the efficacy subgroup analyses defined in Section 10.6, any NS3/4A variant and any NS5A variant are defined as follows, where baseline amino acid variants with ≥ 15% prevalence at certain important signature amino acid positions are considered. Amino acid positions in NS3/4A and NS5A in genotype 2 subjects to be used in subgroup analyses are 155, 156, 168 in NS3 and 24, 28, 30, 92, 93 in NS5A (see Table 8). HCV GT2 subjects with any baseline variant at positions 155, 156, or 168 will be counted as having any NS3/4A variant at baseline. Similarly, HCV GT2 subjects with any baseline variant in positions 24, 28, 30, 92 or 93 will count as having any NS5A variant.

10.10 Patient Reported Outcomes

The following instruments will be used to collect patient reported outcomes (PROs): the EuroQol-5 Dimensions-3 Level (EQ-5D-3L)[5] including the Visual Analog Scale (VAS) and the Fatigue Severity Scale (FSS).

The change from baseline to each applicable post-baseline timepoint in the FSS total score, EQ-5D-3L health index score and VAS score will be summarized descriptively at each visit and for change from baseline to each visit by treatment arm. For each of these scores, mean change from Baseline to Final Treatment Visit and from Baseline to Post-Treatment Week 12 will be compared between treatment arms using an analysis of covariance (ANCOVA) model with treatment arm as a factor and baseline score as a covariate.

Subject's responses to the EQ-5D-3L will be combined into a unique health state using a 5-digit code with 1 digit from each of the 5 dimensions. The EQ-5D-3L states will be converted into a single preference-weighted health utility index score by applying Japan-specific weights, if applicable. The VAS score will be analyzed separately.

The FSS consists of 9 questions using a 7-point Likert scale. A total score is calculated as the average of the individual item responses, with lower scores indicating less impact of fatigue.

Summary statistics (n, mean, SD, median, minimum and maximum) at each visit and for change from baseline to each visit will be provided for the EQ-5D-3L health index score, VAS score and FSS total score. In addition, the number and percentage of subjects who have ever experienced an increase from baseline up through each applicable time point of greater than or equal to 0.7 in the FSS total score will be computed by treatment arm, along with two-sided 95% CI calculated using the normal approximation to the binomial distribution.

For EQ-5D-3L index and VAS scores, no imputation will be performed for missing items. 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.

If a subject starts another treatment for HCV, then all PRO values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses.

11.0 Safety Analysis

11.1 General Considerations

Safety data will be summarized for each treatment arm using the safety population. For safety analyses specified below, comparisons between the treatment arms will be performed.

11.2 Analysis of Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the clinical study report.

11.2.1 Treatment-Emergent Adverse Events

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

11.2.2 Tabulations of Treatment-Emergent Adverse Events

The number and percentage of subjects in each arm with treatment-emergent adverse events will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term. 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 AEs will be presented for each treatment arm consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent adverse event;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to study drug (ABT-493/ABT-530, SOF or RBV);
- Treatment-emergent adverse events of grade 3 or higher;
- Serious treatment-emergent adverse events;
- Serious treatment-emergent adverse events with a "reasonable possibility" of being related to study drug (ABT-493/ABT-530, SOF or RBV);
- Treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent adverse events leading to discontinuation of study drug with a "reasonable possibility" of being related to study drug (ABT-493/ABT-530, SOF or RBV);
- Serious treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent adverse events leading to interruption of study drug;
- Treatment-emergent adverse events of Grade 3 or higher with a "reasonable possibility" of being related to study drug (ABT-493/ABT-530, SOF or RBV);
- Treatment-emergent adverse events leading to RBV dose modification (Arm B);
- Treatment-emergent adverse events leading to death;
- Deaths.

The percentage of subjects experiencing treatment-emergent adverse events and treatment-emergent adverse events with a "reasonable possibility" of being related to study drug, and grade 3 or higher treatment-emergent adverse events will be compared between the two arms using Fisher's exact tests. Only p-values ≤ 0.100 when rounded to three digits will be presented.

Adverse Events by SOC and Preferred Term

Subjects reporting more than one AE for a given preferred term will be counted only once for that term (most severe/highest grade incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one AE within an SOC will be counted only once for that SOC. Subjects reporting more than one AE will be counted only once in the overall total.

The following summaries of AEs by SOC and preferred term will be generated by treatment arm:

- Treatment-emergent adverse events;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to study drug (ABT-493/ABT-530, SOF or RBV);
- Serious treatment-emergent adverse events;
- Serious treatment-emergent adverse events with a "reasonable possibility" of being related to study drug (ABT-493/ABT-530, SOF or RBV);
- Grade 3 or higher treatment-emergent adverse events;
- Treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent adverse events leading to discontinuation of study drug with a "reasonable possibility" of being related to study drug (ABT-493/ABT-530, SOF or RBV);
- Serious treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent adverse events of Grade 3 or higher with a "reasonable possibility" of being related to study drug (ABT-493/ABT-530, SOF or RBV);
- Treatment-emergent adverse events leading to interruption of study drug;
- Treatment-emergent adverse events leading to RBV dose modification (Arm B only);
- Treatment-emergent adverse events leading to death.

The percentage of subjects experiencing treatment-emergent adverse events and treatment-emergent adverse events with a "reasonable possibility" of being related to study drug, and grade 3 or higher treatment-emergent adverse events will be compared between the two arms using Fisher's exact tests. Only p-values ≤ 0.100 when rounded to three digits will be presented. In addition, the number and percentage of subjects experiencing treatment-emergent adverse events and study drug related treatment-emergent adverse event ($\geq 2\%$ and ≥ 2 subjects in either Arm A or Arm B) will be tabulated according to SOC and preferred term.

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 Events by Preferred Term

The number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to preferred term and sorted by overall frequency for the total number of subjects in Arm A. Similar summaries will be provided for Grade 3 or higher treatment-emergent adverse events, treatment-emergent adverse events and treatment-emergent serious adverse event related to study drug (ABT-493/ABT-530, SOF or RBV), and treatment-emergent adverse events of Grade 3 or higher with a "reasonable possibility" of being related to study drug (ABT-493/ABT-530, SOF or RBV). In addition, the number and percentage of subjects experiencing treatment-emergent adverse events and study drug related treatment-emergent adverse event ($\geq 2\%$ and ≥ 2 subjects in either Arm A or Arm B) will be tabulated according to PT and sorted by overall frequency for the total number of subjects in Arm A.

Adverse Events by Maximum Severity Grade Level

Treatment-emergent adverse events and study drug-related treatment emergent adverse events will be summarized by maximum severity grade level of each preferred term. Each adverse event will be assigned a grade level (grade 1, 2, 3, 4, or 5) by the investigator. If a subject has an AE with unknown severity, then the subject will be counted in the severity grade level category of "unknown," even if the subject has another occurrence of

the same event with a severity present. The only exception is if the subject has another occurrence of the same AE with the highest grade level (grade 5). In this case, the subject will be counted under the "Grade 5" category.

Adverse Event by Maximum Relationship

Treatment-emergent adverse events also will be summarized by maximum relationship of each preferred term to study drug (ABT-493/ABT-530, SOF or RBV), as assessed by the investigator. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

Adverse Events by Subgroups

Subgroup analyses will be performed for the safety population. To evaluate the impact of various characteristics, treatment-emergent adverse events will be summarized by treatment arm for each of the following subgroups:

- Sex (male, female)
- Age (< 65 years, ≥ 65 – < 75 years, ≥ 75 years)
- BMI (< 25, ≥ 25 kg/m^2)
- Baseline fibrosis stage (F0 – F1, F2, F3)
- History of cardiovascular disease (yes/no)
- History of diabetes (yes/no)
- Concomitant treatment with liver protectants (yes/no)
- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no)
- Concomitant use of Calcium Channel Blockers (CCBs) (yes/no)

For each subgroup, the adverse event overview will be prepared and the number and percentage of subjects experiencing treatment-emergent adverse events will be summarized by primary MedDRA SOC and preferred term in each treatment arm.

The Breslow-Day test will be used to examine the homogeneity of treatment effect across subgroups for each event type in the AE overview table. The Breslow-Day test will only be performed if there are at least 10 subjects per arm with an event within the subgroup.

Other Adverse Events

The number and percentage of subjects experiencing at least one treatment-emergent adverse event in the search defined below by Product MedDRA Query (PMQ) will be presented overall and by SOC and PT. In addition, a listing of treatment-emergent adverse events for subjects meeting the search criterion will be provided.

"Hepatic Decompensation and Hepatic Failure" (PMQ).

11.2.3 Listing of Adverse Events

The following listings of adverse events will be prepared:

- All serious adverse events (from the time the subject signed the study-specific informed consent through the end of the study),
- Treatment-emergent serious adverse events,
- Treatment-emergent adverse events leading to death,
- Treatment-emergent adverse events leading to discontinuation of study drug,
- Treatment-emergent adverse events leading to study drug interruption,
- Treatment-emergent adverse events leading to RBV dose modification (Arm B only).

11.3 Analysis of Laboratory Data

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

11.3.1 Variables and Criteria Defining Abnormality

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

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, uric acid, cholesterol, total protein, glucose, triglycerides, LDL, HDL, albumin, chloride, bicarbonate, magnesium, total insulin, gamma-glutamyl transferase (GGT), creatinine clearance (calculated using Cockcroft-Gault), and estimated glomerular filtration rate (eGFR) calculated using the modification of diet in renal disease (MDRD) equation defined below.

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

Some of the above laboratory variables are calculated by the laboratory vendor including indirect bilirubin, creatinine clearance, and eGFR by MDRD. The central lab calculates eGFR by MDRD modified for Japanese population using the following equation, where serum creatinine is measured in mg/dL and age is measured in years:

$$eGFR_j \text{ (mL/min/1.73 m}^2\text{)} = 194 \times (\text{Serum Creatinine})^{-1.094} \times (\text{Age})^{-0.287} \times 0.739 \text{ (if Female).}$$

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

$$\text{CrCl (mL/min)} = [(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})]/[\text{serum creatinine (mg/dL)} \times 72].$$

11.3.2 Statistical Methods

The baseline value for clinical laboratory tests will be the last available measurement on or before the day of the first dose of study drug. Values on Day 1 must also be before the time of first dose if time is available. The same baseline value will be used for change to Treatment Period visits and change to Post-Treatment Period visits.

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

Scatterplots of baseline versus final treatment visit for each hematology and chemistry parameter (specified in Table 9) and plots of the mean change in bilirubin (total, direct and indirect) from baseline to each treatment visit by treatment arm will be produced.

The laboratory parameters defined in Table 9 will be assigned a toxicity grade of 1, 2, 3, or 4. The number and percentage of subjects with a maximum toxicity post-baseline grade of 1, 2, 3 or 4 will be summarized for each treatment arm. The maximum post-baseline value must be in a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value to be counted. The summary will also include the number and percentage of subjects with a maximum of at least Grade 3 for all laboratory parameters in Table 9. Comparisons of the percentage of subjects experiencing a value meeting at least Grade 2 between treatment arms will be performed using Fisher's exact tests. Only P values ≤ 0.100 when rounded to three digits will be presented. A listing of all relevant laboratory parameters will be provided for each subject who had an increase to Grade 2 or higher value for any laboratory variable in Table 9.

For ALT and total bilirubin, shift tables from baseline to maximum value in toxicity grade (Table 9) during the treatment period will be created. The shift tables will cross tabulate the frequency of subjects with baseline grade (0, 1, 2, 3, or 4) versus post-baseline

maximum grade (0, 1, 2, 3, or 4). Laboratory values of ALT and total bilirubin within normal ranges are defined as Grade 0.

Table 9. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

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
GGT	> 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	< LLN – 100 g/L	< 100 – 80 g/L	< 80 g/L	--
White blood cells	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Absolute Neutrophil Count	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
Platelet count	< LLN – 75.0 × 10^9/L	< 75.0 – 50.0 × 10^9/L	< 50.0 – 25.0 × 10^9/L	< 25.0 × 10^9/L
INR	> 1 – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	--
Glucose (increased)	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L	> 27.8 mmol/L
Glucose (decreased)	< LLN – 3.0 mmol/L	< 3.0 – 2.2 mmol/L	< 2.2 – 1.7 mmol/L	< 1.7 mmol/L
Creatinine	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 6 × ULN	> 6 × ULN
Creatinine clearance	< LLN – 60 mL/min	< 60 – 30 mL/min	< 30 – 15 mL/min	< 15 mL/min
Cholesterol	> ULN – 7.75 mmol/L	> 7.75 – 10.34 mmol/L	> 10.34 – 12.92 mmol/L	> 12.92 mmol/L
Albumin	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	--

Assessment of Liver Safety

The number and percentage of subjects in each treatment arm with maximum on-treatment lab values meeting the following criteria will be summarized:

- ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN;
- ALT ≥ 3 × ULN and total bilirubin < 2 × ULN;
- ALT > 5 × ULN and total bilirubin < 2 × ULN;
- ALT < 3 × ULN and total bilirubin ≥ 2 × ULN.

The maximum post baseline ratio relative to the ULN will be used to determine if subjects meet the criteria listed above. The ALT and total bilirubin values do not need to be concurrent in order to meet the defined criteria. For ALT and total bilirubin, a subject will be counted if the post-baseline laboratory value meets the above criteria regardless of the baseline laboratory value (i.e., the post-baseline laboratory value does not need to be worse than the baseline laboratory value).

A listing of all ALT, AST, total, indirect and direct bilirubin, ratio of direct to total bilirubin, and alkaline phosphatase values will be provided for each subject who met any of the criteria defined above. The listings will be reviewed to assess bilirubin (e.g., mixed or direct predominance) and temporal relationships for subjects with ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN.

The number and percentage of subjects with post-baseline values during the Treatment Period meeting the following criteria will be summarized:

- ALT > 5 × ULN and ≥ 2 × baseline;
- AST > 5 × ULN and ≥ 2 × baseline;
- Total bilirubin ≥ 2.0 × ULN and > baseline.

As noted above, a post-baseline value must be more extreme than the baseline value to be considered. A separate listing will be provided that presents all lab values for the subjects meeting any of these criteria during treatment.

Laboratory Variables by Subgroups

Laboratory abnormalities of special interest will be assessed for the subgroups defined below:

- Sex (male, female)
- Age (< 65 years, ≥ 65 – < 75 years, ≥ 75 years)
- BMI (< 25, ≥ 25 kg/m^2)
- Baseline fibrosis stage (F0 – F1, F2, F3, F4 (if applicable))
- Concomitant use of Calcium Channel Blockers (CCBs) (yes/no)

These subgroup analyses will be presented for the summary of ALT, AST, alkaline phosphatase, total bilirubin, and hemoglobin by maximum CTCAE grade.

Subgroup analyses will be presented by treatment arm and the Breslow-Day test will be used to examine the homogeneity of treatment effect across subgroups for the percentage of subjects with at least a Grade 2 abnormality and the percentage of subjects with at least a Grade 3 abnormality.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

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

The criteria for potentially clinically significant vital sign findings are presented in Table 10.

Table 10. Criteria for Potentially Clinically Significant Vital Sign Values

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

11.4.2 Statistical Methods

The baseline value for vital signs will be the last measurement on or before the day of the first dose of study drug. The same baseline value will be used for change to Treatment Period visits and change to Post-Treatment Period visits.

Mean changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized 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 on-treatment values meeting the specified criteria for Potentially Clinically Significant (PCS) vital sign values (Table 10) 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 vital sign values for the subjects meeting PCS criteria during treatment.

12.0 Summary of Changes

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

- Added unplanned interim analysis when all subjects reach PT Week 4 or prematurely discontinue from the study to allow for the submission to the PMDA at the time of SVR_4 analysis.
- Added secondary analyses, sensitivity analyses, subgroup analyses, and additional analyses for the submission to the PMDA at the time of SVR_4 analysis.
- Updates were made to the resistance analysis plan to be consistent across the HCV ABT-493/ABT-530 program;
- Updated safety analyses to align across the HCV ABT-493/ABT-530 program;
- Added additional summaries of demographics, baseline characteristics to provide geographic region-specific information (Section 7.1).

13.0 References

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