1.0 Title Page

Statistical Analysis Plan

Study M15-942

An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Combination with Sofosbuvir and Ribavirin in Chronic Hepatitis C (HCV) Infected Subjects Who Have Experienced Virologic Failure in AbbVie HCV Clinical Studies

(MAGELLAN-3)

Date: 28 July 2020

Version 1.0

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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 M15-942.

Study M15-942 evaluates the efficacy and safety of ABT-493/ABT-530, also known as glecaprevir (GLE)/pibrentasvir (PIB), in combination with sofosbuvir (SOF) and ribavirin (RBV) in chronic hepatitis C virus (HCV) genotype (GT) 1 – 6-infected subjects who previously experienced virologic failure in AbbVie HCV clinical studies (designated as AbbVie HCV parent studies), including subjects with compensated cirrhosis and/or human immunodeficiency virus-1 (HIV-1) co-infection and/or post-liver or post-renal transplant. Subjects will receive 12 or 16 weeks of ABT-493/ABT-530 + SOF + RBV, depending on HCV GT, cirrhosis status, and treatment experience with protease inhibitor (PI) and/or NS5A inhibitor (NS5Ai)-containing regimens prior to enrolling in the AbbVie HCV parent studies. Enrollment in Study M15-942 can include subjects who have experienced virologic failure following treatment with AbbVie's ABT-493/ABT-530, or ombitasvir/paritaprevir/ritonavir ± dasabuvir (3D or 2D) in an AbbVie HCV parent study.

This SAP (Version 1.0) provides details to further elaborate the statistical methods outlined in Clinical Study Protocol M15-942 incorporating Amendment 1 dated 31 August 2016, Administrative Change 1 dated 09 February 2017, Amendment 2 dated 06 November 2017, Amendment 2.01 (New Zealand only) dated 20 December 2017 (with an approval date of 12 January 2018), Amendment 2.02 (China only) dated 20 May 2019, Administrative Change 3 (China only) dated 05 June 2020. It describes analysis conventions to guide the statistical programming. Unless noted otherwise, all analyses will be performed using SAS® Version 9.4 (SAS Institute Inc., Carry, NC 27513) or later under the Unix operating system.

The SAP will not be updated in the case of future administrative or minor amendments to the protocol unless the changes have any impact on the analysis of study data.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objectives of this study are to assess the efficacy (by evaluating the percentage of subjects achieving a 12-week post-treatment sustained virologic response, SVR_{12}) and safety of ABT-493/ABT-530 plus SOF and RBV in adults or adolescents with chronic HCV GT1 – 6 infection who previously failed HCV treatment in an AbbVie HCV clinical study, designated as an AbbVie HCV parent study.

The secondary objectives are to assess the rates of HCV on-treatment virologic failure and HCV virologic relapse.

4.2 Design Diagram

Study M15-942 is a Phase 3b, open-label, non-randomized, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in combination with SOF and RBV in HCV GT1 – 6 infected subjects, including subjects with compensated cirrhosis and/or HIV-1 co-infection and/or post-liver or post-renal transplant, who have experienced virologic failure while participating in an AbbVie HCV parent study.

It is anticipated that approximately 50 HCV-infected subjects who have experienced virologic failure following treatment with regimens containing ABT-493/ABT-530, 3D or 2D in one of the AbbVie HCV parent studies will be enrolled. Subjects will be allocated to the 12-week treatment duration (Arm A) or the 16-week treatment duration (Arm B) based on HCV GT, cirrhosis status, and treatment experience with PI and/or NS5Ai-containing regimens prior to enrolling in the AbbVie HCV parent studies, as defined in Table 1.

Table 1. Treatment Arm Allocation in Study M15-942

Patient Population			
Genotype**	**Cirrhotic Status***	**PI and/or NS5Ai-Experienced Prior to the AbbVie HCV Parent Study**	**Study M15-942 Treatment Arm**
1, 2, 4, 5 and/or 6	NC	No	A
3	Any	Any	B
Any	C	Any	B
Any	Any	Yes	B

* NC = non-cirrhotic; C = cirrhotic

** If the subject's HCV GT at Screening is unknown, or if it is mixed and includes GT3, then the subject will be assigned to Arm B (16 weeks), regardless of the cirrhosis status or PI and/or NS5Ai use prior to the AbbVie HCV Parent Study.

Arm A will enroll approximately 5 subjects, and Arm B will enroll approximately 45 subjects. Subjects will receive ABT-493/ABT-530 300 mg/120 mg QD, SOF 400 mg QD, and RBV 600 to 1200 mg daily in two divided doses, orally, for 12 (Arm A) or 16 (Arm B) weeks (Figure 1). Dosing of RBV will be based on baseline age and weight as defined in Table 2.

Scheduled visits for subjects in the Treatment Period consist of Day 1 and Weeks 2, 4, 8, and 12 for all subjects and an additional Week 16 visit for subjects in Arm B. Subjects who complete or prematurely discontinue study drug will be followed for 24 weeks. During the Post-Treatment Period, all subjects will have visits at Post-Treatment Weeks 4, 12, and 24.

Figure 1. Study Schematic

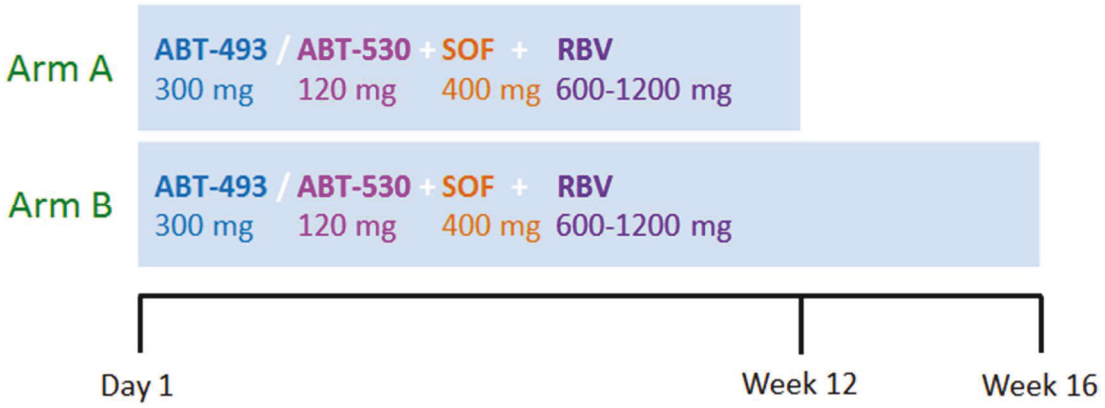

Table 2. Ribavirin Dosing Recommendations

Age at Baseline (Years)	Body Weight at Baseline (kg)	Daily Dose (mg)	Number of 200 mg Tablets Per Period of the Day
≥ 18	< 75	1000	5 tablets
	≥ 75	1200	6 tablets
≥ 12 and < 18	35 – 46	600	3 tablets
	47 – 59	800	4 tablets
	60 – 74	1000	5 tablets
	≥ 75	1200	6 tablets

4.3 Sample Size

This study serves to provide data on using ABT-493/ABT-530 in combination with SOF and RBV as a retreatment option for subjects infected with HCV GT1 – 6 who experienced virologic failure following treatment with regimens containing ABT-493/ABT-530 or 3D or 2D. No formal hypothesis will be tested in this study. The sample size of this study is determined based on the projected number of virologic failures in AbbVie HCV parent studies.

The two-sided 95% confidence intervals (CIs) based on Wilson's score method[1] for a given number of failures are shown in Table 3 for Arm A, B, and overall. The Wilson's score method is expected to be used instead of the normal approximation method because the number of SVR_{12} non-responders is expected to be less than 5 (see Section 10.3).

Table 3. The 95% CIs Using the Wilson's Score Method for a Given Number of Failures

Number of failures for Arm A, B, or overall	Arm A (N = 5)	Arm B (N = 45)	Overall (N = 50)
0	(56.6%, 100.0%)	(92.1%, 100.0%)	(92.9%, 100.0%)
1	(37.6%, 96.4%)	(88.4%, 99.6%)	(89.5%, 99.6%)
2	(23.1%, 88.2%)	(85.2%, 98.8%)	(86.5%, 98.9%)
3	(11.8%, 76.9%)	(82.1%, 97.7%)	(83.8%, 97.9%)
4	(3.6%, 62.4%)	(79.3%, 96.5%)	(81.2%, 96.8%)

4.4 Planned Analyses

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

The primary analysis will occur after all subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinued the study. For the primary analysis, data will be locked after performing appropriate data cleaning. An interim analysis may be conducted for the purpose of regulatory interaction. If there is no interim analysis, the primary analysis and the database lock will occur after all subjects have completed the Post-Treatment Week 24 Visit or prematurely discontinued the study and data cleaning has been performed.

There is no intention of stopping the study early based on efficacy findings from an interim analysis. The intention is to follow all subjects who receive study drug for 24 weeks following treatment.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

5.1.1 Intention-to-Treat (ITT) Population

All enrolled subjects who receive at least one dose of study drug will be included in the ITT population. Efficacy, demographic, baseline characteristics, study drug duration, compliance, concomitant medication and medical history analyses will be performed on the ITT population overall and according to the treatment arm assignment, i.e., subject grouping will be based on the arm to which the subject was assigned.

5.1.2 Modified Intention-to-Treat (mITT) Populations

Sensitivity analyses of SVR_{12} as described in Section 10.5, when applicable, will be performed on the ITT population modified to exclude subjects who do not achieve SVR_{12} for reasons other than virologic failure (mITT-VF).

5.1.3 Safety Population

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

6.0 Analysis Conventions

6.1 Definition of Baseline, Final Treatment, and Final Post-Treatment Assessments

6.1.1 Baseline

The baseline value refers to the last non-missing measurement collected before the first dose of study drug is received.

The protocol specifies that all Day 1 assessments 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

non-missing measurement collected on or before the first day of study drug administration. All Day 1 assessments with time collected must be before the time of first dose to be considered baseline and the last non-missing 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 assessments that are related to a serious adverse event that occurred on the first dose day are excluded when applying this algorithm.

6.1.2 Study Days

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

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 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 (Days Relative to the Last Dose of Study Drug)

Study drug end days are calculated for each time point relative to the last dose of study drug. 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 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 Definition of Analysis Windows

For efficacy analyses of HCV RNA and resistance, the time windows specified in Table 4 and Table 5 describe how these data are assigned to protocol-specified time points during the Treatment and Post-Treatment Periods, respectively. All time points and corresponding time windows are defined based on the date/time of blood sample collection.

For samples of plasma HIV-1 RNA levels and flow cytometry (including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]), the time windows specified in Table 4 describe how data are assigned to protocol-specified time points.

For safety laboratory data, Child-Pugh Score, and vital signs, the time windows specified in Table 4 and Table 6 describe how data are assigned to protocol-specified time points.

If more than one assessment is included in a time window, the assessment closest (except for when used in analyses of SVR) to the nominal time will be used. If there are two observations equally distant to the nominal time, the later 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. For summaries of shifts from baseline, graded laboratory values, and potentially clinically significant vital sign values,

multiple values on the same day will not be averaged; all values will be considered for these analyses.

Table 4. Analysis Time Windows for HCV RNA and Resistance Endpoints, Safety Laboratory and Vital Sign Measurements, and Child-Pugh Scores (Treatment Period)

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Day Range)
Day 1/Baseline[a]	1	≤ 1[a]
Week 2	14	2 to 21
Week 4	28	22 to 42
Week 8	56	43 to 70
Week 12	84	71 to 98
Week 16[b]	112	99 to 126
Final Treatment Visit[c]	2 to ≤ 2 days after last dose of study drug	

a. Day of first dose of study drug.

b. For Arm B 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. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Note: For all windows, data must be on or before Study Drug End Day 2. The result closest to the scheduled time point will be used. Child-Pugh scores are only collected for subjects with compensated cirrhosis at the Screening Visit and End of Treatment Visit (Week 12 Visit for Arm A and Week 16 Visit for Arm B, or Premature Discontinuation Visit).

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

Scheduled Visit[a]	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Day Range)
Post-Treatment Week 4	28	3 to 56
Post-Treatment Week 12	84	57 to 126
Post-Treatment Week 24	168	127 to 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}. For all windows, data must occur after Study Drug End Day 2. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Table 6. Analysis Time Windows for Safety Laboratory and Vital Sign Measurements and Child-Pugh Score (Post-Treatment Period)

Scheduled Time[a]	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 999
Final Post-Treatment Visit[a]	> 2 days after last dose of study drug	

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

b. 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. Study Drug End Day 0 is defined as the day of the last dose of study drug.

Note: The result closest to the scheduled time point will be used. For all windows, data must occur after Study Drug End Day 2. Vital signs are collected at Post-Treatment Week 4 only; hematology, chemistry, urinalysis, and coagulation panels are collected at Post-Treatment Week 4 Visit or at Post-Treatment Discontinuation Visit if subject discontinues during the Post-Treatment Week 4 window. Child-Pugh scores are only collected for subjects with compensated cirrhosis at Post-Treatment Weeks 12, 24, and the Premature Discontinuation Visit.

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.

For analyses of SVR, subjects' missing visit values 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 is missing an HCV RNA value within the appropriate SVR window after performing backward imputation, then this value will be imputed with an HCV RNA value from a local laboratory if present; otherwise, the HCV RNA value will be missing. Subjects with missing HCV RNA data in the analysis window, after imputations, will be imputed as a failure.

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 present in the appropriate time period, then the local laboratory value will be used to assess post-treatment relapse and on-treatment virologic failure.

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

The ITT population will be used to summarize demographics, baseline characteristics, medical history and previous, concomitant, and post-treatment medications; data will be summarized across all subjects and by assigned 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. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum). For categorical variables, the number of missing observations will be displayed, if applicable, on the summary tables. Percentages will be calculated based on the number of non-missing observations.

Continuous demographic variables include age, weight, height, waist circumference, and body mass index (BMI). Categorical demographic variables include sex, race, Black race (Black or non-Black), ethnicity, age category (< 65 or ≥ 65 years; < 75 or ≥ 75 years), BMI category (< 30, or ≥ 30 kg/m^2), country, and geographic region (North America, Europe, Asia, or rest of world [ROW]).

When defining geographic region, sites in the United States and Canada will be grouped under North America; sites in Switzerland, Germany, Sweden, Spain, Russia and the United Kingdom will be grouped under Europe; sites in China and South Korea will be grouped under Asia; sites in Brazil, Australia and New Zealand will be grouped together as ROW.

Continuous baseline characteristics include baseline $\log_{10}$ HCV RNA level, creatinine clearance (Cockcroft-Gault calculation), eGFR (using the modification of diet in renal disease [MDRD] formula), platelet count, albumin, GGT, APRI, FIB-4, AST, ALT, total, direct, and indirect bilirubin, and homeostasis model of assessment – insulin resistance (HOMA-IR) for all subjects.

Categorical baseline characteristics include:

- HCV GT (1, 2, 3, 4, 5, 6, mixed, or unknown) and available subtype (as determined by the central laboratory);

- HCV GT (1, 2, 3, 4, 5, 6, mixed, or unknown) and available subtype (as determined by phylogenetic analysis, if available, or by the central laboratory if phylogenetic analysis is not available)
- DAA-containing regimen received in the AbbVie HCV parent study (ABT-493/ABT-530, 3D or 2D);
- Type of treatment response for AbbVie HCV parent study (on-treatment non-responder, breakthrough, post-treatment relapse, or unknown/other);
- Prior AbbVie HCV parent study number;
- Previous treatment experience prior to enrolling in the AbbVie HCV parent study:
  - Treatment naïve/DAA-naïve
  - Treatment experienced, PI-experienced only
  - Treatment experienced, NS5Ai-experienced only
  - Treatment experienced, PI- and NS5Ai-experienced
  - Treatment experienced, NS5Bi-experienced only
  - Treatment experienced, NS5Bi- and PI-experienced
  - Treatment experienced, NS5Bi- and NS5Ai-experienced
  - Treatment experienced, NS5Bi-, PI- and NS5Ai-experienced
- HCV mono-infected vs. HCV/HIV-1 co-infected;
- Cirrhotic vs. non-cirrhotic;
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, or F4);
- Baseline HCV RNA level ($< 1{,}000{,}000$, $\geq 1{,}000{,}000$ to $< 2{,}000{,}000$, $\geq 2{,}000{,}000$ IU/mL);
- 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);
- Injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no);
- Use of stable opiate substitution (yes/no);

- Tobacco use (current, former, never, or unknown);
- Alcohol use (current, former, never, or unknown);
- Concomitant use of proton pump inhibitors (PPIs) [yes/no];

For subjects with cirrhosis, the following will be summarized:

- Baseline Child-Pugh Score (5, 6, or > 6).

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

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 but biopsy score is absent, 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 7.

Table 7. 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 < 0.59
F3	3	4	≥ 9.6 to < 12.5	0.59 to < 0.75
F4	4	≥ 5	≥ 12.5	≥ 0.75

* 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 fibrosis stage. Discordance between FibroTest and APRI will require FibroScan or liver biopsy to determine subject fibrosis stage.

Presence or absence of cirrhosis will be determined as collected in EDC ("What is the subject's cirrhosis status?" – "cirrhotic" or "non-cirrhotic").

Baseline Child-Pugh score will be calculated for subjects with cirrhosis according to 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.

** None: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

Baseline APRI and FIB-4 are defined as the equations below. Subjects 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.

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

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

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

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

The central laboratory calculates the eGFR by MDRD based on the following formula except for data collected from the sites in China:

$$\text{eGFR (mL/min/1.73 m}^2) = 175 \times (\text{Serum Creatinine in mg/dL})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if Black or African American}).$$

The central laboratory calculates the eGFR by the MDRD formula modified for the Chinese population (C-MDRD) for data collected from the sites in China using the following formula:

$$\text{eGFR (mL/min/1.73 m2)} = 175 \times (\text{Serum Creatinine in mg/dL})^{-1.234} \times (\text{Age})^{-0.179} \times (0.79 \text{ if female}).$$

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 9.

Table 9. 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. 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. 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 "Concomitant Medications and Supplements" eCRF.

Prior medications will be divided into the following categories:

- Prior HCV medications taken by subjects who were treatment-experienced prior to entering the AbbVie HCV parent study (collected on the "Previous HCV Therapy (Prior to the AbbVie HCV Parent Study)" eCRF);
- Prior HCV medications taken during the AbbVie HCV Parent Study (collected on the "Screening Failure" eCRF as "Treatment Regimen for AbbVie HCV Parent Study");
- All other non-HCV and non-HIV prior medications for all treated subjects.

The number and percentage of subjects taking prior medications, concomitant medications, and post-treatment HCV medications will be summarized by generic drug name based on the WHO Drug Dictionary.

If this study enrolls HCV/HIV co-infected subjects, prior HIV medications (collected on the "Prior and Concomitant HIV Therapy" eCRF) and concomitant HIV medications (entered as "Other HIV medications" on the "Concomitant Medications and Supplements" eCRF) will not be included in the summaries mentioned above but will be presented as data listings for HCV/HIV co-infected subjects.

8.0 Subject Disposition

The number and percentage of subjects who screen failed for any reason, and for each screen fail 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.

- Subjects enrolled in this study;
- Subjects who took at least one dose of study drug;
- Subjects who completed all study drugs;
- Subjects who completed all DAAs (including those who discontinued RBV)
- Subjects who prematurely discontinued all study drugs;
- Subjects who completed the study;
- Subjects who prematurely discontinued from the study;

The number and percentage of subjects who discontinued all study drugs 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 will be calculated for:

- Subjects with interruption of all DAAs;
- Subjects with interruption of any DAA;
- Subjects with interruption of ABT-493/ABT-530;
- Subjects with interruption of SOF;
- Subjects with RBV dose modification.

DAA interruptions and RBV dose modifications will be summarized by treatment arm and overall. Reasons for study drug interruptions and RBV dose modifications will be presented in the CSR listings.

9.0 Study Drug Duration and Compliance

Study drug duration and compliance will be summarized on the ITT population by treatment arm and overall.

9.1 Study Drug Duration

Study drug duration is defined for each subject as the last study drug dose date minus the first study drug dose date plus 1 day.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for study drug duration.

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
- 91 to 105 days
- > 105 days

In addition, the number and percentage of subjects with study drug duration of ≥ 77 days for the 12-week arm or study drug duration ≥ 103 days for the 16-week arm will be summarized.

9.2 Compliance

For each kit (ABT-493/ABT-530, SOF, and RBV), the total number of tablets dispensed and returned is recorded for each of the three components of the study drug (ABT-493/ABT-530, SOF, and RBV). The compliance of a subject for each component

of the study drug during the Treatment Period will be calculated as the percentage of tablets taken relative to the total expected to be taken, which will be derived according to the duration of that subject's Treatment Period (date of last dose of study drug – date of first dose of study drug + 1). For ABT-493/ABT-530 and SOF, study drug interruptions recorded on the eCRF will not be subtracted from the treatment duration of that study drug. For RBV compliance, RBV dose modifications and interruptions (modification to 0 mg) as recorded on the RBV Dose Modifications eCRF will be used to modify the total number of RBV tablets expected to be taken. If a subject is not able to return any of the dispensed kit, that subject's compliance will be regarded as missing.

A subject is considered to be compliant for a component of the study drug (ABT-493/ABT-530, SOF, or RBV) if the percentage is between 80% and 120%. Compliance will be calculated for each subject and each component and will be summarized with the mean, median, standard deviation, minimum, and maximum by treatment arm and overall. A listing of compliance for each subject on each component will also be provided. The percentage of compliant subjects for each component will be summarized by treatment arm and overall, based on data as observed. Subjects with missing values for compliance will not be included in the denominator.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

All efficacy analyses will be performed on the ITT population by treatment arm and overall, unless otherwise specified. To support the primary analysis, sensitivity analyses will also be conducted using the mITT-VF population.

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

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 of 15 IU/mL or greater.

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**; if a subject meets both definitions of Breakthrough and EOT failure, he or she will be categorized as Breakthrough only.

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 study drug (up to and including the SVR_{12} window) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment, 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 Post-Treatment Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment, excluding reinfection.

Virologic failure = **On-treatment virologic failure** or **$Relapse_{overall}$**

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 77 days or greater for Arm A and 103 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 NS3/4A, and/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 NS3/4A, and/or NS5A, and/or NS5B 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$_{12}$ Non-Response

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

1. On-treatment virologic failure;
2. HCV reinfection;

3. Relapse$_{12}$;
4. 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 < 77 days for Arm A, or < 103 days for Arm B] and did not meet the **On-treatment virologic failure or HCV reinfection** definitions);
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;
2. HCV reinfection;
3. Relapse$_{12}$;
4. Relapse$_{24}$;
5. 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 < 77 days for Arm A, or < 103 days for Arm B] and did not meet the **On-treatment virologic failure**, **HCV reinfection, Relapse$_{12}$**, or **Relapse$_{24}$** definitions);
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]).

For the reasons for SVR_{12} and SVR_{24} nonresponse defined above, subjects are only to be counted in one category in the order shown above.

10.2 Handling of Multiplicity

No multiplicity adjustment is needed for this study because there is no hypothesis testing.

10.3 Primary Efficacy Analysis

The primary efficacy endpoint is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The number and percentage of subjects in the ITT population achieving SVR_{12} will be calculated along with a two-sided 95% CI using the normal approximation to the binomial distribution, unless the number of SVR_{12} non-responders is less than 5, where the Wilson's score method[1] will be used to calculate the CI instead.

A summary of reasons for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, other) will be provided. A listing of subjects who do not achieve SVR_{12} by reason for non-response will also be provided.

10.4 Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- The percentage of subjects with on-treatment virologic failure;
- The percentage of subjects with $Relapse_{12}$.

The number and percentage of subjects with on-treatment virologic failure and $Relapse_{12}$ in the ITT population will be summarized along with two-sided 95% Wilson score CIs.

10.5 Sensitivity Analyses for SVR

As sensitivity analyses, the number and percentage of subjects in the mITT-VF population achieving SVR_{12} will be summarized along with two-sided 95% CIs using the normal approximation to the binomial distribution and the Wilson's score method.

A different CI from that used for the primary analysis will be calculated for the primary endpoint of SVR_{12} based on the ITT population as a sensitivity analysis. If the number of SVR_{12} non-responders is ≥ 5, then the two-sided 95% CI using Wilson's score method will be calculated. If the number of SVR_{12} non-responders is < 5, the two-sided 95% CI using the normal approximation to the binomial distribution will be calculated.

Listings of subjects excluded from the mITT-VF population will be provided, as applicable.

10.6 Efficacy Subgroup Analysis

The percentage of subjects with SVR_{12} in the ITT population will be presented. Two-sided 95% Wilson score CIs will also be presented for the following subgroups if there are at least 10 subjects in the subgroup:

- HCV genotype (1, 2, 3 4, 5, 6, mixed, or unknown) (based on final HCV genotype and subtype determination specified in Section 10.8);
- DAA-containing regimen received in the AbbVie HCV parent study (ABT-493/ABT-530, 3D or 2D);
- Previous treatment experience prior to enrolling in the AbbVie HCV parent study:
  - Treatment naïve/DAA-naïve
  - Treatment experienced, PI-experienced only
  - Treatment experienced, NS5Ai-experienced only
  - Treatment experienced, PI- and NS5Ai-experienced
  - Treatment experienced, NS5Bi-experienced only
  - Treatment experienced, NS5Bi- and PI-experienced

- Treatment experienced, NS5Bi- and NS5Ai-experienced
- Treatment experienced, NS5Bi-, PI- and NS5Ai-experienced

- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, or F4);
- Baseline HCV RNA level (< 1,000,000, ≥ 1,000,000 to < 2,000,000, or ≥ 2,000,000 IU/mL).

10.7 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized for the ITT population:

- 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_4;
- The percentage of subjects with SVR_{24};
- The percentage of subjects who relapse after achieving SVR_{12} (**$Relapse_{24}$**).
- The percentage of subjects with virologic failure through Post-Treatment Week 24 (i.e., the SVR_{24} non-responders due to **on-treatment virologic failure** or **$Relapse_{overall}$**).

For each of the above endpoints, a two-sided 95% CI using Wilson's score method will be calculated along with the number and percentage of subjects. Imputations for missing data will be performed as described in Section 6.3 for all the additional endpoints listed above except the first one.

For the ITT population, a summary of the subjects who completed treatment and relapsed (defined as **$Relapse_{overall}$**) will be prepared displaying the number of subjects relapsing at any timepoint and by the SVR visit window where the first relapse occurred (within the SVR_4, SVR_{12}, or SVR_{24} window or after the SVR_{24} window); subject numbers will be listed. A similar summary 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_{24} will be summarized by reason for non-response (as defined in Section 10.1) for the ITT population. A listing of subject numbers and reason for non-response will be prepared.

The concordance between SVR_{12} and SVR_{24} will be assessed for the overall population (across genotype and 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_{24} out of all subjects who did not achieve SVR_{12}. Similarly, the concordance between SVR_4 and SVR_{12} will be summarized for the overall population.

10.8 Resistance Analyses

10.8.1 HCV Drug-Resistance Analyses

For all subjects, full length NS3/4A and NS5A will be sequenced from baseline samples by next generation sequencing (NGS). For all subjects who experience virologic failure (on-treatment virologic failure or $Relapse_{overall}$ as defined in Section 10.1), full length NS3/4A, NS5A and NS5B genes from the first sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. For all other subjects who do not achieve SVR_{12} or SVR_{24} (for non-virologic failure reasons as defined in Section 10.1) but have a post-treatment time point with HCV RNA ≥ 1000 IU/mL, full length NS3/4A, NS5A and NS5B genes from the first post-treatment sample with HCV RNA ≥ 1000 IU/mL will also be sequenced by NGS.

For all subjects who do not achieve SVR_{12} or SVR_{24}, a listing by subject that includes HCV genotype/subtype, reason for SVR_{12} or SVR_{24} non-response, baseline resistance data availability, and key baseline characteristics will be produced by treatment arm.

For each DAA target, signature amino acid positions and the key subset of amino acid positions for the respective inhibitor class are shown in Table 10. Appropriate subtype-specific prototypic reference sequences will be used for comparison with sequences from samples.

Table 10. Signature Amino Acid Positions and the Key Subsets of Amino Acid Positions

Target	Signature Amino Acid Positions	Key Subset of Amino Acid Positions
GT1 NS3	36, 43 (GT1a only), 54, 55, 56, 80, 107, 122, 132 (GT1a only), 155, 156, 158, 168, 170, 175 (GT1b only)	155, 156, 168 (all GTs)
GT2, 3, 4, 5, 6 NS3	36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3 only), 168	
GT1 NS5A	24, 28, 29, 30, 31, 32, 54 (GT1b only), 58, 62, 92, 93	24, 28, 30, 31, 58, 92, 93 (all GTs)
GT2, 3, 4, 5, 6 NS5A	24, 28, 29, 30, 31, 32, 58, 92, 93	
GT1, 2, 3, 4, 5, 6 NS5B	96, 142, 159, 237, 282, 289, 320, 321	282

Included time points for analyses of samples from subjects who do not achieve SVR_{12} are 1) the sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1000 IU/mL, and 2) 24 weeks post-DAA treatment, provided that resistance-associated substitutions were detected at the time of failure/discontinuation.

The following definitions will be used in the resistance analyses:

- Baseline polymorphism: a polymorphism by NGS in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on polymorphism frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3, NS5A, or NS5B).
- Post-baseline substitution: an amino acid substitution in a post-baseline time point sample that was not detected at baseline (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the post-baseline sample.

- Enriched variant: a variant present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20]
- Treatment-emergent substitution: A post-baseline substitution or an enriched variant.
- Substitution at signature amino acid position: a substitution in a post-baseline sample observed at ≥ 2% prevalence within a subject's viral population that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3/4A, NS5A, or NS5B).

Analysis 1

The following analyses will be performed for all subjects, separated by arm, HCV genotype/subtype, and previous treatment experience prior to enrolling in the AbbVie HCV parent study (including total):

- A listing of baseline polymorphisms (2% detection threshold) at signature amino acid positions for each DAA target (NS3, NS5A, and NS5B) in the ITT population. HCV genotype/subtype and treatment outcome (SVR_{12} or reason for SVR_{12} non-response) will also be displayed for each subject.
- The number and percentage of subjects with baseline polymorphisms at signature amino acid positions at detection thresholds of 2% and 15% for subjects in the ITT population. This analysis includes prevalence of each baseline polymorphism, and a summary of the number of subjects with polymorphisms in NS3 only, NS5A only, 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, and any in NS3 + NS5A + NS5B.
- Total number and percentage of subjects in the ITT population with baseline polymorphisms ***in the key subset of amino acid positions*** at detection thresholds of 15% for subjects in the ITT population. This analysis summarizes the number of subjects with polymorphisms in NS3 only, NS5A only, 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, and any in NS3 + NS5A + NS5B.

Analysis 2

The impact of baseline polymorphisms at the ***key subset of amino acid positions*** on treatment outcome (the SVR_{12} rate) will be assessed for the **mITT-VF** population by presenting the SVR_{12} rates for the following groups, using detection thresholds of 2% and 15%, separated by arm, HCV genotype/subtype (including total), and previous treatment experience prior to enrolling in the AbbVie HCV parent study:

- in NS3 only versus none in NS3, NS5A, or NS5B
- in NS5A only versus none in NS3, NS5A, or NS5B
- in NS5B only compared to none in NS3, NS5A, or NS5B
- any in both NS3 and NS5A versus none in NS3 or NS5A
- any in both NS3 and NS5B versus none in NS3 or NS5B
- any in both NS5A and NS5B versus none in NS5A or NS5B
- any in each of NS3, NS5A and NS5B versus none in NS3, NS5A, or NS5B
- any in NS3 versus none in NS3
- any in NS5A versus none in NS5A
- any in NS5B versus none in NS5B
- any in NS3 or NS5A or NS5B versus none in NS3, NS5A, or NS5B

Analysis 3

The following listings will be produced for subjects who do not achieve SVR_{12} or SVR_{24} and have post-baseline resistance data available. HCV genotype/subtype and reason for SVR_{12} or SVR_{24} non-response will be displayed for each subject by treatment, and previous treatment experience prior to enrolling in the AbbVie HCV parent study.

- Listing by subject and time point of all *treatment-emergent substitutions* relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B).
- Listing by subject and time point of all *substitutions at signature amino acid positions* in a post-baseline time point relative to the appropriate prototypic reference amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B).

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV sequences from baseline samples for 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 a region of NS5B by the Central lab (Covance) and/or from phylogenetic analysis of the full length NS3/4A NS5A, and/or NS5B sequences performed by AbbVie. If the phylogenetic analysis is available, 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 is available, then the Inno-LIPA assay results will be used to categorize the subject.

This subtype information will be presented in summaries of efficacy subgroup analyses.

A summary of HCV 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 if any differ.

10.8.2 HIV Drug-Resistance Analysis

If an HCV/HIV-1 co-infected subject develops a confirmed, plasma HIV-1 RNA level ≥ 500 copies/mL after starting the study, the subject's HIV-1 PR, RT, and/or IN

sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays. If available and incorporated in the SAS datasets, these results will be presented as data listings.

11.0 Safety Analysis

11.1 General Considerations

Safety data will be summarized using the safety population. Data will be summarized for the overall population.

11.2 Analysis of Adverse Events

Adverse events (AEs) 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.

AIDS-Defining Conditions (ADC) will be presented separately (Section 11.3) and will be excluded from all analyses of AEs described below in the rest of Section 11.2.

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with an onset date that is after the first dose of study drug and no more than 30 days after the last dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. If an incomplete onset date was collected for an AE, 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

Adverse Event Overview

An overview of AEs will be presented that consists of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE;
- Treatment-emergent AEs with a "reasonable possibility" of being related to ABT-493/ABT-530;
- Treatment-emergent AEs with a "reasonable possibility" of being related to SOF;
- Treatment-emergent AEs with a "reasonable possibility" of being related to RBV;
- Treatment-emergent AEs of Grade 3 or higher;
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to ABT-493/ABT-530;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to SOF;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to RBV;
- Treatment-emergent AEs leading to discontinuation of all study drugs;
- ABT-493/ABT-530-related treatment-emergent AEs leading to discontinuation of all study drugs;
- SOF-related treatment-emergent AEs leading to discontinuation of all study drugs;
- RBV-related treatment-emergent AEs leading to discontinuation of all study drugs;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to ABT-493/ABT-530;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to SOF;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to RBV;
- Serious treatment-emergent AEs leading to discontinuation of all study drugs;
- Treatment-emergent AEs leading to interruption of study drug;

- Treatment-emergent AEs leading to RBV dose modifications (RBV dose increased or reduced);
- Treatment-emergent AEs leading to death;
- Deaths.

Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects with treatment-emergent AEs will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) for the summaries listed below. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

- Treatment-emergent AEs;
- Treatment-emergent serious AEs;
- Treatment-emergent serious AEs with a "reasonable possibility" of being related to ABT-493/ABT-530;
- Treatment-emergent serious AEs with a "reasonable possibility" of being related to SOF;
- Treatment-emergent serious AEs with a "reasonable possibility" of being related to RBV;
- Treatment-emergent AEs leading to discontinuation of all study drugs;
- ABT-493/ABT-530-related treatment-emergent AEs leading to discontinuation of all study drugs;
- SOF-related treatment-emergent AEs leading to discontinuation of all study drugs;
- RBV-related treatment-emergent AEs leading to discontinuation of all study drugs;
- Treatment-emergent AEs leading to death.

Subjects reporting more than one AE for a given PT will be counted only once for that term (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.

If a subject has an AE with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same AE with a relationship assessment of "reasonable possibility." In this case, the subject will be counted under the "reasonable possibility" category.

A listing of treatment-emergent AEs grouped by SOC and PT with subject numbers will be created for the overall safety population.

Adverse Events by PT

The following summaries of treatment-emergent AEs tabulated according to PT and sorted by the overall frequency across the two treatment arms will be generated:

- Treatment-emergent AEs;
- Treatment-emergent AEs with a "reasonable possibility" of being related to ABT-493/ABT-530;
- Treatment-emergent AEs with a "reasonable possibility" of being related to SOF;
- Treatment-emergent AEs with a "reasonable possibility" of being related to RBV;
- Treatment-emergent AEs of Grade 3 or higher;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to ABT-493/ABT-530;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to SOF;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to RBV.

Subjects reporting more than one AE for a given PT 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 will be counted only once in the overall total.

Adverse Events by Maximum Severity Grade Level

Treatment-emergent AEs will be summarized by maximum severity grade level of each PT tabulated by SOC. Each AE 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. The same analyses will be performed for treatment-emergent AEs with a "reasonable possibility" of being related to the study drug, separated by ABT-493/ABT-530, SOF, and RBV.

11.2.3 Adverse Events of Special Interest

Adverse events of special interest include the following:

- Hepatic decompensation/hepatic failure events, identified using the AbbVie Product MedDRA Query (PMQ) of "Hepatic Decompensation and Hepatic Failure."
- Hepatocellular carcinoma (HCC) events, identified using the MedDRA PTs of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent.

For the hepatic decompensation/ hepatic failure AE of special interest, the number and percentage of subjects experiencing at least one treatment-emergent AE in the search will be presented by SOC and PT and across all SOCs/PTs. In addition, a by-subject listing of treatment-emergent AEs meeting the search criterion will be provided.

For the hepatocellular carcinoma AE of special interest, a by-subject listing of all post-baseline (i.e., including both treatment-emergent and non-treatment emergent) AEs meeting the search criterion will be provided.

11.2.4 Listing of Adverse Events

The following listings of AEs will be prepared:

- All serious AEs (from the time the subject signed the study-specific informed consent through the end of the study),
- Treatment-emergent serious AEs,
- Treatment-emergent AEs leading to discontinuation of all study drugs,
- Treatment-emergent AEs leading to interruption of study drug,
- Treatment-emergent AEs leading to RBV dose modification,
- Treatment-emergent AEs leading to death.

11.3 AIDS Defining Conditions

A by-subject listing of reported AIDS-Defining Conditions (ADCs), as specified in the protocol, will be provided.

11.4 Analysis of Laboratory Data

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

11.4.1 Variables and Criteria Defining Abnormality

Hematology variables to be summarized 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 to be summarized 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, cholesterol, total protein, glucose, triglycerides, albumin, chloride, bicarbonate, magnesium, total insulin, gamma-glutamyl transferase (GGT), creatinine clearance (calculated using Cockcroft-Gault formula), and eGFR (calculated using MDRD equation).

Urinalysis variables to be summarized include: specific gravity and pH.

The definitions of toxicity grades for laboratory parameters are presented in Table 11.

Table 11. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN
AST	> 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	--

11.4.2 Statistical Methods

The baseline value for clinical laboratory tests will be the last non-missing 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 changes to Treatment Period visits and changes to Post-Treatment Period visits.

Visit Values

For each protocol-specified laboratory parameter, values at each visit (baseline and post-baseline, including applicable post-treatment visits) will be summarized with the sample size, mean, standard deviation, minimum, median, and maximum.

Change from Baseline

For each laboratory parameter listed in Section 11.4.1, changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized with the sample size, baseline mean; visit mean; and change from baseline mean, standard deviation, minimum, median, and maximum.

Shift Tables

Individual changes in the laboratory parameters listed in Section 11.4.1 will be tabulated using shift tables. Laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used for each sample. Shift tables from baseline to minimum value and maximum value during the Treatment Period will be created. For each parameter, the shift tables will cross tabulate the frequency of subjects with baseline values below/within the normal range to maximum above the normal range and with baseline values within/above the normal range to minimum below the normal range.

Maximum Toxicity Grade

The laboratory parameters listed in Table 11 will be assigned a toxicity grade of 1, 2, 3, or 4. The number and percentage of subjects with a maximum toxicity grade of 1, 2, 3

or 4 during the Treatment Period will be tabulated. To be counted, the post-baseline value must have a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value. For each laboratory parameter in Table 11, the summary will also include the number and percentage of subjects with a post-baseline maximum of at least Grade 3. A listing of all relevant laboratory parameters will be provided for each subject who had an increase to Grade 2 or higher for any laboratory variable in Table 11.

Assessment of Hepatic Laboratory Values

The number and percentage of subjects with laboratory values meeting the following criteria during treatment will be summarized:

- Post-nadir (preceding value is lower than the subsequent value) ALT > 5 × ULN (regardless of grade change);
- Total bilirubin ≥ 2 × ULN and > baseline (i.e., a post-baseline value must be more extreme than the baseline value to be considered);
- Post-nadir ALT > 3 × ULN and total bilirubin > 2 × ULN;
- Post-nadir ALT > 3 × ULN and total bilirubin ≤ 2 × ULN.

Four listings (one for each bullet above) of all hepatic laboratory values including 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 the criterion defined above.

Hepatic Laboratory Abnormalities of Interest

Among the events assessed under "Assessment of Hepatic Laboratory Values," the following criteria are of interest:

- Confirmed post-nadir ALT > 5 × ULN;
- Post-nadir ALT > 3 × ULN and a concurrent total bilirubin > 2 × ULN with a direct/total bilirubin ratio > 0.4.

To support the assessment of hepatic laboratory abnormalities of interest, the following potential events will be summarized:

- Confirmed post-nadir ALT > 5 × ULN;
- Post-nadir ALT > 3 × ULN and total bilirubin > 2 × ULN and direct/total bilirubin ratio > 0.4.

Two listings (one for each bullet) of all hepatic laboratory values including 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 the criterion defined above.

For the **assessments of hepatic laboratory values** and **hepatic laboratory abnormalities of potential interest**, the maximum ratio relative to the ULN will be used to determine if subjects meet any of the criteria listed above. The ALT and total bilirubin values do not need to be concurrent in order to meet the defined criteria in statistical summaries. For ALT, the post-baseline value must represent an increase from the first nadir (including baseline) to be counted. First nadir is defined as the last value prior to the first increase. For 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), except where noted above. A confirmed post-nadir increase in ALT is defined as two consecutive values of ALT > 5 × ULN after nadir, either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement. A single post-nadir ALT value of greater than 5 × ULN followed by lost to follow-up (no additional ALT values) also will be considered (i.e., will not require confirmation). The ratio of direct to total bilirubin will be calculated using the same date/time sample corresponding to the total bilirubin elevation.

11.5 Analysis of Vital Signs Data

11.5.1 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 (PCS) vital sign findings are presented in Table 12.

Table 12. 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

11.5.2 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.

For each vital sign parameter listed in Section 11.5.1, values at each visit (baseline and post-baseline, including applicable post-treatment visits) will be summarized with the sample size, mean, standard deviation, minimum, median, and maximum.

The number and percentage of subjects with on-treatment values meeting the specified criteria for PCS vital sign values (Table 12) will be summarized. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A separate

listing will be provided that presents all vital sign values for the subjects meeting PCS criteria during treatment.

11.6 Analysis of HIV-1 RNA and Flow Cytometry

If this study enrolls HCV/HIV co-infected subjects, plasma HIV-1 RNA and flow cytometry data will be presented in subject data listings.

12.0 Summary of Changes

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

1. The planned analyses (Section 4.4) have been updated for better clarity.
2. The category cutoffs of baseline HCV RNA level have been changed (Section 7.1 and Section 10.6) to reflect current HCV project standards.
3. Certain efficacy subgroup variables have been changed (Section 10.6) because of the small sample size of the study and the current HCV project standards.
4. The resistance analyses (Section 10.8) have been updated to reflect current HCV project standards.
5. Analyses for HCV/HIV co-infected subjects (Section 7.3, Section 10.8.2, Section 11.3) have been deleted because of the anticipated small sample size of the HIV-1 co-infected subjects; subject-level data will be presented in listings.
6. For subgroups of treatment experience prior to enrolling in the AbbVie HCV parent study, "treatment-naïve" and "treatment-experience, DAA-naïve" are combined as "treatment-naïve/DAA-naïve" (Section 7.1 and Section 10.6) because of the small sample size of the study and because the recommended regimens of ABT-493/ABT-530 are the same for treatment-naïve and DAA-naïve GT1, 2, 4, 5, 6 subjects.

7. The percentage of subjects with virologic failure through Post-Treatment Week 24 has been added to additional efficacy analyses (Section 10.7) to reflect current HCV project standards.
8. Safety analyses will only be performed for the overall population (Section 11.1) because of the small sample size of the study and the current HCV project standards.
9. Analyses for vital signs have been updated (Section 11.5.2) according to the current HCV project standards.

13.0 References

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.