1.0 Title Page

Statistical Analysis Plan

STUDY M13-576

A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy (ABT-493 and/or ABT-530) in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection

Date: 23 Aug 2019

Version 1.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the AbbVie Statistics Department for study Protocol M13-576. This study is designed to assess resistance and durability of response to AbbVie direct-acting antiviral (DAA) therapy ABT-493, also known as glecaprevir (GLE), and/or ABT-530, also known as pibrentasvir (PIB), in subjects who participated in prior AbbVie Phase 2 or 3 clinical studies for the treatment of chronic hepatitis C virus (HCV) infection.

The SAP provides details to further elaborate the statistical methods outlined in Clinical Study Protocol M13-576 Amendment 3 (October 2017), and describes analysis conventions to guide the statistical programming. The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis. Analyses will be performed using SAS® Version 9.4 (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 as follows:

- Assess the durability of response for subjects who achieved SVR_{12} with a regimen including ABT-493 and/or ABT-530.
- Assess the persistence of specific HCV amino acid substitutions associated with drug resistance in subjects who experienced virologic failure.

The secondary objectives of the study are as follows:

- Summarize medical events related to progression of liver disease including but not limited to events of hepatic decompensation, change in Child-Pugh classification, liver transplantation, hepatocellular carcinoma, and/or death.

- Summarize results of the following laboratory tests and scores: FibroTest, APRI, IP-10, alpha fetoprotein (if collected under a protocol version prior to protocol Amendment 3), FibroScan, and liver biopsy.

4.2 Study Design

This Phase 2/3, multicenter study will be conducted in subjects who received at least one dose of an ABT-493- and/or ABT-530-containing regimen at any dose level in a prior AbbVie Phase 2 or 3 study for the treatment of chronic HCV and elect to enroll in this study. The subject must have completed the follow-up period of the prior eligible AbbVie study. It is anticipated that approximately 400 subjects will participate in this study. An attempt will be made to enroll all virologic failures who will not receive immediate re-treatment with a regimen containing ABT-493/ABT-530.

At the Day 1 Visit, subjects will provide written (signed and dated) informed consent prior to any study specific procedures being performed. The investigator will evaluate whether the subject meets all of the eligibility criteria prior to enrollment in this rollover study. Subjects will be followed for approximately 3 years following their last dose of DAA in the previous AbbVie HCV clinical study; the 3 years will be inclusive of any post-treatment period in the prior study, as well as any gap between the end of the prior study and enrollment into this study. Once a subject has reached 3 years post-DAA therapy, participation in this study will be completed, except for subjects enrolled with virologic failure who receive re-treatment with a new HCV antiviral regimen that does not contain ABT-493/ABT-530. Subjects who are re-treated with HCV regimens other than ABT-493/ABT-530 will have only one further assessment for treatment outcome 12 weeks after stopping that therapy or earlier in cases of virologic failure. Subjects who have not been re-treated will return to the study site for their scheduled visits on an outpatient basis as described in Section 5.3.1 of the protocol until approximately 3 years after their last dose of DAA in the previous clinical study.

4.3 Sample Size

No sample size determination was conducted for this study. The objective of the study is to characterize the persistence of amino acid substitutions in subjects enrolled in AbbVie DAA studies who experienced virologic failure, and the durability of response in subjects who achieved SVR_{12}. Thus, the number of subjects enrolled in the current trial will be partially based on the number of subjects who experienced virologic failure in prior studies with AbbVie DAA therapies and subsequently agree to participate in the current trial.

The sample size was increased under protocol Amendment 2 to allow for inclusion of a representative sample of subjects from additional studies added in Amendment 2.

4.4 Interim Analysis

An interim analysis was conducted in 2016 to support the ABT-493/ABT-530 initial marketing applications (NDA/MAA). There is no multiplicity adjustment for the interim analysis as no hypothesis testing was performed. The final analysis will be conducted when all subjects enrolled in the study have completed the follow-up period.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

All enrolled subjects include subjects who may have received re-treatment prior to enrollment in Study M13-576. The full analysis set is defined as all subjects who received an ABT-493- and/or ABT-530-containing regimen at any dose level in a previous AbbVie Phase 2 or 3 study and enroll in this study without receiving re-treatment prior to enrolling in this study. Therefore, subjects who received re-treatment prior to enrollment in this study will be excluded from the full analysis set. In addition, subjects who enrolled without meeting inclusion criterion 2 (e.g., subjects who were treated with SOF + DCV in the prior AbbVie study, Study M13-594) will be excluded from the full analysis set.

A listing of subjects excluded from the full analysis set will be provided.

All demographic, efficacy, and safety analyses described in this SAP will be conducted on the full analysis set, unless otherwise specified.

5.2 Variables Used for Stratification of Randomization

There is no randomization in this study.

6.0 Analysis Conventions

6.1 Definition of Baseline and Final Assessment

Definition of Baseline and Final Treatment Visit Value (Previous Study)

Baseline is defined as the last non-missing measurement before the first dose of study drug **in the previous study**. The final treatment visit value is defined as the last non-missing measurement collected after baseline and within 2 days of the last dose of study drug **in the previous study**.

Definition of Day 1 and Study Days (Study M13-576)

Day 1 refers to the Day 1 visit in Study M13-576. Study days in Study M13-576 are calculated for each time point relative to the Day 1 visit in this study. Study days are negative values when the time point of interest is prior to Day 1. Study days are positive values when the time point of interest is after Day 1. There is no Study Day 0. Study Days will be used to summarize hematology, clinical chemistry, and additional laboratory tests (IP-10, INR, and serum albumin) collected within this study.

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

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

drug end days will be used to define the SVR windows from the previous study, and HCV RNA and resistance endpoints within this study.

6.2 Definition of Analysis Windows

For efficacy analyses of HCV RNA and resistance, the time windows specified in Table 1 describe how efficacy data are assigned to analysis (or SVR) windows during the Post-Treatment Period of the previous study and in Study M13-576. All time points and corresponding time windows are defined based on the blood sample collection date.

For safety laboratory data collected within Study M13-576, the time windows specified in **Table 2** 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 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, the last value in the window will be used.

If multiple measurements are made on the same day, the average of the values will be used to calculate descriptive statistics, except baseline values (see Section 6.1).

Table 1. Analysis Time Windows for HCV RNA and Resistance Endpoints

Scheduled Visit	Nominal Day (Study Drug End Day)	Time Window (Study Drug End Days Range)
Post-Treatment Week 4 (SVR_4)	28	3 to 56
Post-Treatment Week 12 (SVR_{12})	84	57 to 126
Post-Treatment Week 24 (SVR_{24})	168	127 to 210
Post-Treatment Week 36	252	211 to 294
Post-Treatment Week 48	336	295 to 378
Post-Treatment Week 60	420	379 to 462
Post-Treatment Week 72	504	463 to 546
Post-Treatment Week 84	588	547 to 630
Post-Treatment Week 96	672	631 to 714
Post-Treatment Week 108	756	715 to 798
Post-Treatment Week 120	840	799 to 882
Post-Treatment Week 132	924	883 to 966
Post-Treatment Week 144	1008	967 to 1050
Post-Treatment Week 156	1092	1051 to 9,999

Note: The result closest to the scheduled time point will be used, except for SVR endpoints, where the last HCV RNA value in the window will be used.

Table 2. Analysis Time Windows for Study M13-576 Protocol Defined Assessments, other than HCV RNA and Resistance

Scheduled Visit	Nominal Day (Study Day)	Time Window (Study Days Range)
Day 1	1	1
Month 3	91	2 to 136
Month 6	181	137 to 271
Month 12	361	272 to 451
Month 18	541	452 to 631
Month 24	721	632 to 811
Month 30	901	812 to 991
Month 36	1081	992 to 9,999

Note: A month is defined as 30 days. The closest value in the window will be used.

6.3 Missing Data Imputation

The values of SVR_4, SVR_{12}, and SVR_{24} will be derived from the previous study as needed.

For subjects in the full analysis set, 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 the analyses of SVR and virologic failure. 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.

6.4 Overall Type-I Error Control

There is no hypothesis testing for the efficacy analyses, therefore no multiplicity adjustment will be performed for the study.

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

Demographics, baseline characteristics, medical history, and previous/concomitant medications will be summarized on the full analysis set, unless otherwise specified.

7.1 Demographic and Baseline Characteristics

Demographics as captured on the eCRF in Study M13-576 will be summarized. Other demographics (e.g., baseline BMI) and baseline characteristics as captured in the previous study will be summarized.

Demographics will include:

- Age (continuous; < 65 or ≥ 65 years; < 75 or ≥ 75 years), per Study M13-576 database;
- Sex, per Study M13-576 eCRF;
- Ethnicity, per Study M13-576 eCRF;
- Race, per Study M13-576 eCRF;
- Baseline BMI (continuous; < 30 or ≥ 30 kg/m^2), per previous study;
- Country, per Study M13-576 database;
- Region (Europe, North America, or rest of world), per Study M13-576 database;
- Previous study number, per Study M13-576 eCRF;
- Previous assigned treatment duration (8, 12, or 16 weeks), per previous study.

Baseline characteristics will include:

- HCV genotype (1, 2, 3, 4, 5, and 6) and subtype (1a, 1b, 2a, 3a, etc.), per previous study;
- IL28B genotype (CC, CT, or TT; CC or non-CC), per previous study;
- Treatment status prior to previous study (naïve or experienced [PRS, NS5A naïve/PI experienced, NS5A experienced/PI naïve, NS5A experienced/PI experienced]), per previous study;
- Baseline log_{10} HCV RNA levels (continuous) and (< 1,000,000, ≥ 1,000,000 to < 2,000,000, ≥ 2,000,000 IU/mL), per previous study;
- Baseline cirrhosis status in prior study, per Study M13-576 eCRF;
- Baseline HIV-1/HCV coinfection status, per previous study;
- Tobacco and alcohol use; as captured on the Study M13-576 eCRF;
- Baseline injection drug use status, per previous study;
- Baseline status on use of stable opiate substitution, per previous study;
- Concomitant use of proton pump inhibitors (PPIs) during prior study.

Summary statistics (N, mean, median, standard deviation (SD), and range) will be generated for continuous variables (e.g., age and BMI) and the number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses, as recorded in the Study M13-576 medical history dataset. 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 Previous Treatment and Concomitant Medications

The number and percentage of subjects taking prior HCV medications (prior to entry in the previous study) or concomitant medications as captured on the eCRFs in Study M13-576 will be summarized by generic drug name based on the WHO Drug Dictionary.

The study drug regimen (e.g., ABT-493 300 mg QD + ABT-530 120 mg QD or ABT-493/ABT-530 300 mg/120 mg) and treatment duration (e.g., 8, 12, or 16 weeks; if the assigned treatment duration was extended, then the final assigned treatment duration will be counted) assigned in the previous studies will be summarized for each regimen and duration combination. The regimens will be summarized, with the respective final assigned duration (8, 12, or 16 weeks), as:

- ABT-450/r + ABT-530 + RBV
- ABT-493 200 mg QD + ABT-530 40 mg QD
- ABT-493 200 mg QD + ABT-530 80 mg QD
- ABT-493 200 mg QD + ABT-530 120 mg QD
- ABT-493 200 mg QD + ABT-530 120 mg QD + RBV
- ABT-493 300 mg QD + ABT-530 120 mg QD
- ABT-493 300 mg QD + ABT-530 120 mg QD + RBV
- ABT-493/ABT-530 300 mg/120 mg QD

Medications related to the treatment of HCV will be collected in the PT Period (including previous study and Study M13-576) and will be summarized by generic drug name separately for subjects in the full analysis set and for subjects excluded from the full analysis set. A post-treatment medication for the treatment of HCV is defined as any medication taken on or after the last dose of study drug in the previous study and entered as "Post treatment HCV medications" on the eCRF in Study M13-576 or similarly on the eCRF in the prior study.

8.0 Subject Disposition

The number of subjects for each of the following categories will be summarized overall and by investigator, based on all enrolled subjects.

- Enrolled subjects;
- Subjects who completed the study;
- Subjects who discontinued from the study;
- Subjects who are in the full analysis set.

The number and percentage of subjects in the full analysis set who discontinued from the study will be summarized by reason (all reasons) and by primary reason as recorded on the eCRF.

The duration of follow-up will be summarized both in days and in months for the full analysis set. Duration of follow-up in days is defined for each subject as the last HCV RNA measurement date in Study M13-576 minus the last study drug dose date (in the previous study) plus 1 day. Duration of follow-up in months will be calculated as duration days/30.5. Descriptive statistics (mean, SD, median, minimum, and maximum) will be presented for each measure of duration of follow-up.

A listing of subjects who are excluded from the full analysis set will be provided.

9.0 Study Drug Duration and Compliance

There is no study drug dispensed in this study.

10.0 Efficacy Analyses

10.1 General Considerations

General Considerations

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.

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

Definitions for Efficacy Endpoints

A confirmed quantifiable post-treatment value is defined as any two consecutive post-treatment HCV RNA measurements ≥ LLOQ. In all relapse analyses, completion of treatment is defined as study drug duration ≥ 52 days for 8-week regimens, ≥ 77 days for 12-week regimens, and ≥ 105 days for 16-week regimens.

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 (derived from the previous study).

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 (derived from the previous study).

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 (derived from the previous study).

$Relapse_{12}$ = 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 above based on study drug duration in the previous study), excluding reinfection (derived from the previous study).

$Relapse_{late}$ = confirmed HCV RNA ≥ LLOQ at any time after the SVR_{12} assessment time point for a subject who achieved SVR_{12} and has post-SVR_{12} HCV RNA data available, excluding reinfection (derived from both studies).

$Relapse_{overall}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in Study M13-576 for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment, excluding reinfection.

$SVR_{overall}$ = HCV RNA < LLOQ between the end of treatment and up to and including the last HCV RNA measurement collected in Study M13-576 without any confirmed quantifiable (≥ LLOQ) post-treatment value before value.

Only subjects who have at least one post-treatment HCV RNA value will be included in analyses of relapse. 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$_{late}$**, **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.

In the efficacy analyses, **SVR$_{12}$** and **Relapse$_{12}$** will be based on the values from the previous study. **Relapse$_{late}$**, **Relapse$_{overall}$** and **SVR$_{overall}$** will be derived based on HCV RNA data collected both in the previous study and in this study. Subjects with reinfection will be identified using data from both studies.

10.2 Efficacy Analyses

The following efficacy analyses will be conducted on the full analysis set including data up to the last follow-up in this study prior to any HCV re-treatment. For subjects in the

full analysis set, HCV RNA measurements taken after the start of another anti-viral HCV treatment (after completion of AbbVie DAA treatments in previous study) will be excluded from the analyses.

The number and percentage of subjects in the full analysis set who achieved SVR_{12} in the previous study will be summarized overall and by study. A listing of subjects in the full analysis set who did not achieve SVR_{12} will be provided.

Based on the full analysis set, the number and percentage of subjects who maintain SVR in this study among those who achieved SVR_{12} in the previous study will be summarized, overall and by visit. Study visits will be displayed as Post-Treatment Weeks 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156. For each visit, the denominator will indicate the number of subjects in the full analysis set who achieved SVR_{12} and have HCV RNA data within the corresponding visit window. For the overall summary, the denominator will indicate the number of subjects in the full analysis set who achieved SVR_{12}. Overall maintenance of SVR is defined as no confirmed HCV RNA ≥ LLOQ after the SVR_{12} timepoint (from the previous study) through the last HCV RNA measurement in this study. Confirmation of quantifiable HCV RNA values can occur among any two consecutive HCV RNA values; either both during the same visit window or at the end of a visit window and in the next window. The visit window corresponding to the first occurrence of the confirmed HCV RNA ≥ LLOQ will be counted as having the failure. If the last available value in the study is ≥ LLOQ, then the subject will be considered as not maintaining SVR (i.e., will not require confirmation). The summary will include the subject number and the visit window corresponding to the first occurrence of quantifiable HCV RNA.

Among the subjects in the full analysis set who achieved SVR_{12} in the previous study, a listing of subjects who do not maintain SVR will be provided with subject number, previous study number, the reason (relapse or reinfection) for not maintaining SVR, days from study drug end date to relapse or reinfection, and whether the relapse or reinfection occurs before or after enrolling into this study.

The number and percentage of subjects who relapse (see **Relapse$_{late}$** definition) at any time up to the last follow-up in this study will be summarized out of subjects in the full analysis set who achieved SVR_{12} in the previous study. In addition, the number and percentage of subjects in the full analysis set who relapsed anytime (see **Relapse$_{overall}$** definition) or have new HCV infection (see definition of reinfection) anytime will be summarized.

The time to relapse (**Relapse$_{overall}$**) or new HCV infection (i.e., reinfection) from the end of DAA treatment for subjects who achieved HCV RNA < LLOQ at the end of treatment in the previous study will be displayed graphically using Kaplan-Meier curves. Similarly, the time to relapse (**Relapse$_{late}$**) or new HCV infection (i.e., reinfection) from the SVR_{12} time point for the subset of subjects who achieved SVR_{12} in the previous study will also be displayed graphically using Kaplan-Meier curves. These summaries will be separate for subjects who have probable relapse as distinguished from subjects who have probable new HCV infection (i.e., reinfection) based on the definitions of relapse and reinfection in Section 10.1.

For the first Kaplan-Meier curve among subjects with final on-treatment HCV RNA < LLOQ, time to event will be measured as the number of days from the last dose of study drug (in the previous study) to event or censoring time. Subjects who do not relapse or were not reinfected will be censored at the date corresponding to the last available HCV RNA measurement.

For the second Kaplan-Meier curve among subjects who had achieved SVR_{12}, time to event will be measured as the number of days from the nominal day of SVR_{12} assessment to event or censoring time. Subjects who do not relapse or were not reinfected will be censored at the date corresponding to the last available HCV RNA measurement.

For both subjects in the full analysis set and subjects excluded from the full analysis set, a listing of subjects who are re-treated will be provided specifying whether the re-treatment occurs before or after enrolling into the study, prior AbbVie regimen, HCV re-treatment regimen, and SVR_{12} outcome.

10.3 Resistance Analyses

The following subjects in the full analysis set will have resistance testing conducted: (1) those with on-treatment virologic failure (VF) in the previous study; (2) those with post-treatment relapse prior to enrollment in Study M13-576; and (3) those who become viremic (with HCV) during Study M13-576.

For all subjects entering Study M13-576 who meet the criteria for resistance testing above (i.e., have virologic failure), listings will be provided to summarize HCV subtype, time of VF, HCV RNA levels, time point(s) sequenced, and assessment of possibility of new infection.

Only samples with an HCV RNA level of ≥ 1,000 IU/mL will undergo sequence analysis in order to allow accurate assessment of the products of amplification. For subjects who experience VF before or during Study M13-576, the sample closest in time after the failure with an HCV RNA level ≥ 1,000 IU/mL will be used if the HCV RNA level at the time of VF is < 1,000 IU/mL.

The regions of interest for next-generation sequencing (NGS) from all evaluated time points in this study are those encoding complete NS3/4A and/or NS5A (based on regimen received in the earlier study). Subtype-specific prototypic reference strains for sequence analyses will be utilized.

For each DAA target, signature amino acid positions and a key subset of amino acid positions are listed in Table 3. Appropriate subtype-specific prototypic reference sequences will be used for comparison with sequences from samples.

Table 3. Signature Amino Acid Positions and the Key Subset 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)	155, 156, 168 (all GTs)
GT 2-6 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)
GT 2-6 NS5A	24, 28, 29, 30, 31, 32, 58, 92, 93	

The following definitions will be used in the resistance analyses:

- Baseline sample: sample collected before the first dose of DAA study drug in the previous study.
- 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 (NS3/4A or NS5A).
- Polymorphism/substitution at a signature amino acid position: polymorphism (relative to reference) present in a baseline sample or substitution (relative to baseline) present in post-baseline sample at a signature amino acid position.
- 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 substitution: substitution 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 substitution.

- Substitution at signature amino acid position: 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 or NS5A).

For subjects with virologic failure who have resistance testing conducted:

- A listing by subject of all baseline polymorphisms (2% detection threshold) at signature amino acid positions will be provided for each DAA target (NS3/4A and NS5A).
- A listing by subject and time point of all treatment-emergent substitutions relative to the baseline amino acid sequences will be provided for each DAA target (NS3/4A and NS5A).
- A listing by subject and time point of all post-baseline substitutions at signature amino acid positions relative to the appropriate subtype-specific reference amino acid sequence will be provided for each DAA target (NS3/4A and NS5A).

11.0 Safety Analyses

Safety analyses will be presented for subjects in the full analysis set.

As this is a non-drug interventional study, only serious adverse events that the investigator considers reasonably related to interventional study procedures (i.e., venipunctures) or those considered reasonably related to ABT-530 and/or ABT-493 drug exposure in the prior study by the investigator will be reported as serious adverse events.

Collected adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class (SOC) and preferred term (PT).

11.1 Analysis of Adverse Events

11.1.1 Tabulations of Serious Adverse Events

Serious adverse event data will be summarized and presented using primary MedDRA SOCs and PTs according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the clinical study report. The SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC.

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

A summary of serious adverse events by SOC and PT will be generated.

11.1.2 Listing of Adverse Events and Deaths

Listings of all serious (as defined in the protocol) adverse events and deaths (from the time the subject signed the study-specific informed consent through the end of the study) will be provided.

11.2 Analysis of Medical Events Related to Liver Disease or HCV Infection

Any events related to liver disease progression and/or HCV infection that are considered to be clinically significant by the investigator and begin or worsen after Day 1 will be captured on the appropriate Medical Events eCRF(s). These significant events include but are not limited to: the development of cirrhosis, events indicative of hepatic decompensation, changes in Child-Pugh classification, liver transplantation, hepatocellular carcinoma, and/or death.

The number and percentage of subjects who reported each and any of the following medical events will be summarized:

- development of cirrhosis,
- hepatic decompensation - variceal bleeding,
- hepatic decompensation - new ascites,
- hepatic decompensation - spontaneous bacterial peritonitis,
- hepatic decompensation - hepatic encephalopathy,
- hepatic decompensation - hepato-renal syndrome,
- hepatic decompensation - hepatic hydrothorax,
- other evidence of hepatic decompensation,
- change in the Child-Pugh category,
- hepatocellular carcinoma,
- occurrence of liver transplantation,
- death,
- other.

Listings of each medical event will be provided. In addition, listings of any liver diagnostic testing that is collected (e.g., liver biopsy or FibroScan scores) will be provided.

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.

Hematology variables include: platelet count

Chemistry variables include: total bilirubin, alpha-fetoprotein, gamma glutamyl transferase (GGT), alpha2-macroglobulin, AST, ALT, haptoglobin, and apolipoprotein A1.

Additional variables include: FibroTest, IP-10, INR, and serum albumin.

11.3.1 Statistical Methods

Each protocol-specified laboratory parameter will be summarized at each applicable study visit (e.g., Day 1, Month 3, Month 6, etc. as defined in the protocol) with the sample size, visit mean, SD, minimum, median, and maximum.

11.4 Analysis of Vital Signs and Weight

Not applicable; vital signs and weight are not collected in this study.

12.0 Summary of Changes

Table 4. SAP Version History Summary

Version	Date	Summary
1.0	19 August 2019	Original version

The following changes were made between the latest version of the protocol and SAP Version 1.0:

- Under resistance analyses, only listings are planned to be provided due to the limited number of virologic failures treated with ABT-493 and/or ABT-530;
- IL28B is no longer included in resistance listings due to its limited utility in predicting virologic failure;
- The number and percentage of subjects who have new HCV infection (re-infection) will be summarized for all subjects in the full analysis set, rather than for the subset of subjects in the full analysis set who had achieved SVR_{12} as the outcomes of relapse and maintenance of SVR are of main interest rather than the rate of reinfection.