1.0 Title Page

Statistical Analysis Plan

Study M15-592

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Treatment-Naïve and Treatment-Experienced, Non-Cirrhotic Asian Adults with Chronic Hepatitis C Virus Genotype (GT) 1 to GT6 Infection With or Without Human Immunodeficiency Virus Co-Infection

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Version 1.0

2.0 Table of Contents

List of Tables

List of Figures

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the AbbVie Statistics and Statistical Programming Departments for Study M15-592. Study M15-592 evaluates the efficacy, safety, and pharmacokinetics of ABT-493/ABT-530 in non-cirrhotic, chronic hepatitis C virus (HCV) genotype (GT) 1 to GT6-infected Asian adult subjects with or without human immunodeficiency virus (HIV) co-infection who are HCV treatment-naïve or treatment-experienced with interferon (IFN) (alpha, beta or pegylated-IFN [pegIFN]) with or without ribavirin (RBV) OR sofosbuvir (SOF) with RBV with or without IFN.

This SAP provides details to further elaborate statistical methods as outlined in Clinical Study Protocol M15-592 incorporating Administrative Change No. 1 dated 02 October 2017 and describes analysis conventions to guide the statistical programming. Analyses will be performed using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

This SAP does not include the analysis plan for the pharmacokinetic data.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objectives of this study are to compare, among the combined group of GT1 to GT6-infected subjects, among the GT1-infected subjects, and among the GT2-infected subjects, the percentage of subjects achieving SVR_{12}, (HCV RNA < lower limit of quantification [LLOQ] 12 weeks after the last actual dose of study drug) to a historical SVR_{12} rate and to assess the safety following 8 or 16 weeks of treatment with the ABT-493/ABT-530 combination regimen in treatment-naïve and treatment-experienced non-cirrhotic adults with chronic HCV GT1 to GT6 infection with or without HIV co-infection.

The secondary objectives are to assess:

- The percentage of subjects with on-treatment HCV virologic failure;
- The percentage of subjects with post treatment relapse of HCV infection;
- The percentage of HCV/HIV co-infected subjects achieving SVR_{12}.

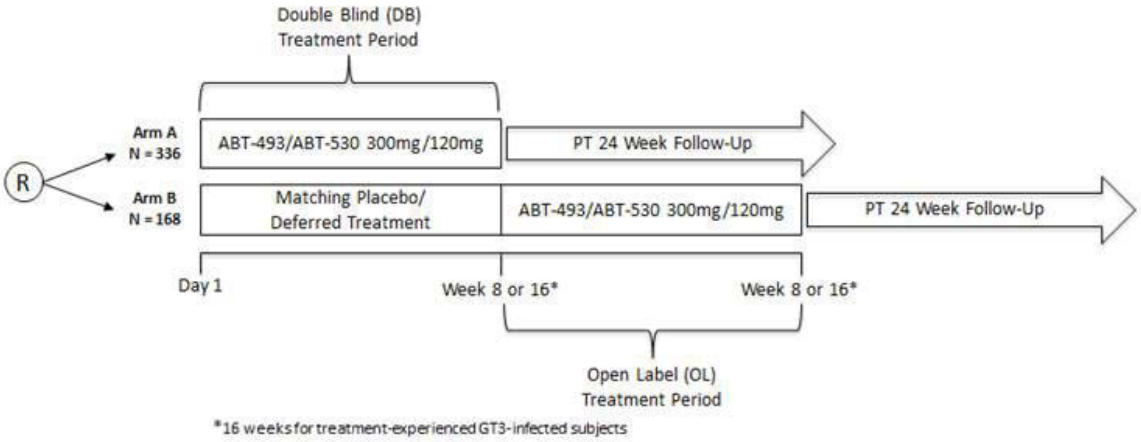
An additional objective is to assess the pharmacokinetics of ABT-493 and ABT-530 in Asian HCV-infected adults.

4.2 Design Diagram

This is a Phase 3, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in non-cirrhotic chronic HCV GT1 to GT6-infected Asian adult subjects with or without HIV co-infection who are HCV treatment-naïve or treatment-experienced with IFN (alpha, beta or pegIFN) with or without RBV OR sofosbuvir with RBV with or without IFN. This study consists of a Double-Blind (DB) Treatment Period, an Open-Label (OL) Treatment Period, and a Post-Treatment (PT) Period. The study schematic is presented in Figure 1.

The study is designed to enroll approximately 504 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with scientific and ethical considerations. A minimum of 150 GT1-infected subjects, a minimum of 150 GT2-infected subjects and approximately 60 GT3, 4, 5 or 6-infected subjects from China will be enrolled into this study. Approximately 105 GT1-infected subjects and approximately 39 GT2-infected subjects will also be enrolled into this study from the regional Asian countries of South Korea and Singapore. Of the approximately 504 subjects, a maximum of 50 HCV/HIV co-infected subjects will be enrolled.

Figure 1. Study Schematic



Chronic HCV GT1 – 6 infected adults without underlying cirrhosis will be enrolled into one of two treatment arms:

Arm A: ABT-493/ABT-530 300 mg/120 mg QD for 8 or 16 weeks

Arm B: Matching Placebo for 8 or 16 weeks followed by open-label ABT-493/ABT-530 300 mg/120 mg QD for 8 or 16 weeks

All subjects in this study are to be non-cirrhotic. Treatment experienced GT3-infected subjects will receive 16 weeks of treatment in the DB and/or OL Treatment Period; all other subjects will receive 8 weeks of treatment in the DB and/or OL Treatment Period.

In China, subjects will be randomized to receive active treatment (Arm A) or placebo (Arm B) in a 2:1 ratio for each of the GT1 and GT2-infected groups and the combined GT3 to GT6 infected group. In each regional Asian country, each of the GT1 and GT2 infected groups will be randomized in a 2:1 ratio.

Subjects who are randomized to Arm B will receive open-label ABT-493/ABT-530 300 mg/120 mg QD for 8 or 16 weeks following the DB Treatment Period.

Randomization of subjects will be stratified by geographic region (China, Singapore and South Korea), genotype (GT1, GT2, combined GT3 – 6), and HCV/HIV co-infection status (yes, no).

4.3 Sample Size

It is planned to enroll a total of approximately 504 subjects. In China, approximately 150 GT1-infected subjects will be randomized to receive active treatment (Arm A) or placebo (Arm B) in a 2:1 ratio; approximately 150 GT2-infected subjects will be randomized in a 2:1 ratio; and approximately 60 GT3, 4, 5, or 6-infected subjects will be randomized in a 2:1 ratio. Across Singapore and South Korea, approximately 105 GT1-infected subjects and approximately 39 GT2-infected subjects will be randomized to Arm A and Arm B; randomization will occur within each regional country in a 2:1 ratio. A maximum of 50 of the 504 subjects will have HCV/HIV co-infection across all countries. The expected approximate number of subjects by subpopulation is presented in Table 1.

For the first primary endpoint, with a sample size of 336 GT1 – 6-infected subjects in the active treatment arm (Arm A) and assuming that 97% of these subjects will achieve SVR_{12}, this study has greater than 95% power to show non-inferiority to a historical control regimen, using a threshold of 90%, based on a 1-sample test for superiority using EAST 6.3. The threshold of 90% was based on a historical SVR_{12} rate of 96% and a 6% non-inferiority margin (see Section 4.3.1). To establish efficacy, the lower bound of a 2-sided 95% confidence interval (CI) for the SVR_{12} rate must be greater than 90% (based on a normal approximation of a single binomial proportion CI). No adjustment for dropouts is applicable because subjects who do not have data at PT Week 12 (after imputing) are counted as failures for SVR_{12}.

For the second primary endpoint, with a sample size of 170 GT1-infected subjects in the active treatment arm (Arm A) and assuming that 97% of these subjects will achieve SVR_{12}, this study has 90% power to show non-inferiority to a historical control regimen, using a threshold of 91%, based on a 1-sample test for superiority using EAST 6.3. The

threshold of 91% was based on a historical SVR_{12} rate of 97% and a 6% non-inferiority margin (see Section 4.3.1). To establish efficacy, the lower bound of a 2-sided 95% CI for the SVR_{12} rate must be greater than 91% (based on a normal approximation of a single binomial proportion CI). No adjustment for dropouts is applicable because subjects who do not have data at PT Week 12 (after imputing) are counted as failures for SVR_{12}.

For the third primary endpoint, with a sample size of 126 GT2-infected subjects in the active treatment arm (Arm A) and assuming that 96% of these subjects will achieve SVR_{12}, this study has greater than 80% power to show non-inferiority to a historical control regimen, using a threshold of 89%, based on a 1-sample test for superiority using EAST 6.3. The threshold of 89% was based on a historical SVR_{12} rate of 95% and a 6% non-inferiority margin (see Section 4.3.1). To establish efficacy, the lower bound of a 2-sided 95% CI for the SVR_{12} rate must be greater than 89% (based on a normal approximation of a single binomial proportion CI). No adjustment for dropouts is applicable because subjects who do not have data at PT Week 12 (after imputing) are counted as failures for SVR_{12}.

Table 1. Summary of Approximate Subject Numbers Expected by Subpopulation

Sub-Population	DB Active	DB Placebo	Total
GT1	**170**	**85**	**255**
China	100	50	150
HCV/HIV Co-infected	*10*	*5*	*15*
Not HCV/HIV Co-infected	*90*	*45*	*135*
Asian Regional Countries	70	35	105
HCV/HIV Co-infected	*6*	*3*	*9*
Not HCV/HIV Co-infected	*64*	*32*	*96*
GT2	**126**	**63**	**189**
China	100	50	150
HCV/HIV Co-infected	*10*	*5*	*15*
Not HCV/HIV Co-infected	*90*	*45*	*135*
Asian Regional Countries	26	13	39
HCV/HIV Co-infected	*2*	*1*	*3*
Not HCV/HIV Co-infected	*24*	*12*	*36*
GT3 – 6	**40**	**20**	**60**
China	40	20	60
HCV/HIV Co-infected	*4*	*2*	*6*
Not HCV/HIV Co-infected	*36*	*18*	*54*
Total GT1 – 6	**336**	**168**	**504**
China	240	120	360
HCV/HIV Co-infected	*24*	*12*	*36*
Not HCV/HIV Co-infected	*216*	*108*	*324*
Asian Regional Countries	96	48	144
HCV/HIV Co-infected	*8*	*4*	*12*
Not HCV/HIV Co-infected	*88*	*44*	*132*

4.3.1 Justification of Success Criteria for Primary Endpoints

For the first, second, and third primary endpoints, SVR_{12} thresholds of 90%, 91%, and 89%, respectively were chosen to align with the historical control rates (and corresponding non-inferiority margins) used in the Global Phase 3 studies.

In the Global Phase 3 study of GT1-infected subjects without cirrhosis (Study M13-590), a historical control rate of 97% was used with a non-inferiority margin of 6%, resulting in a threshold of 91%. The historical control SVR_{12} rate for non-cirrhotic subjects receiving ombitasvir/paritaprevir/ritonavir and dasabuvir (3-DAA) ± RBV in the 3-DAA Phase 3 trials among subjects dosed according to the United States Package Insert (USPI) and the Summary of Product Characteristics (SmPC) recommendations was 97% (870/894 patients),[1] with no difference between treatment-naïve and treatment-experienced subjects. Of note, the historical SVR_{12} rate of 97% for the 3-DAA ± RBV regimen is identical to that of SOF/ledipasvir for 12 weeks in GT1-infected non-cirrhotic subjects (ION-1, ION-2, and ION-3).[2]

In the Global Phase 3 study of GT2-infected subjects without cirrhosis (Study M15-464), a historical control rate of 95% was used with a non-inferiority margin of 6%, resulting in a threshold of 89%. This historical control rate was based on the regimen of SOF + RBV for 12 weeks of treatment (Table 2).

Table 2. Historical Data for SOF + RBV for 12 Weeks, GT2-Infected Non-Cirrhotic Patients

Study	SVR_{12} n/N (%)
FISSION	59/61 (97%)
POSITRON	85/92 (92%)
FUSION	26/29 (90%)
VALENCE	59/63 (95%)
GS-US-334-011812[3]	132/136 (97%)
Total	**361/381 (95%)**

GT = genotype; RBV = ribavirin; SOF = sofosbuvir; SVR_{12} = sustained virologic response 12 weeks postdosing
Note: SVR_{12} rates from Sovaldi® (sofosbuvir) Tablets United States Package Insert.[4]

The Global Phase 3 study of GT3-infected subjects without cirrhosis (Study M13-594) was a randomized, active-controlled study, with the active control of SOF + daclatasvir (DCV) for 12 weeks. The assumption of an SVR_{12} rate of 98% for the active control arm was based on the ALLY-3 study.[5] Among non-cirrhotic subjects in the ALLY-3 trial, 98% of treatment-naïve subjects and 92% of treatment-experienced subjects achieved SVR_{12} after 12 weeks of SOF + DCV treatment. Only treatment-naïve subjects were enrolled in Study M13-594. A 6% non-inferiority margin was used in Study M13-594.

The Global study of non-cirrhotic subjects which includes GT6 as well as GT4 and GT5 patients (Study M13-583) was an open-label single-arm study. The analysis of the primary endpoint (SVR_{12}) was descriptive only.

The historical SVR_{12} rate for the first primary endpoint of the current study was calculated as a weighted average of the historical rates from the Global Phase 3 studies using the expected percentage of subjects for each GT, as indicated in Table 3. The expected SVR_{12} rate for the first primary endpoint was calculated similarly, using the expected rates for the test regimens in the Global Phase 3 studies. To align with the non-inferiority margin used in the Global studies, a non-inferiority margin of 6% was chosen for this study. Therefore, the percentage of subjects with SVR_{12} will be non-inferior to the historical SVR_{12} rate of 96% if the lower confidence bound of the 2-sided 95% CI for the percentage is > 90%.

The historical and expected SVR_{12} rates for the second primary endpoint of the current study align with those from the Global Phase 3 Study M13-590. To align with the non-inferiority margin used in the Global studies, a non-inferiority margin of 6% was chosen for this study. Therefore, the percentage of subjects with SVR_{12} will be non-inferior to the historical SVR_{12} rate of 97% if the lower confidence bound of the 2 sided 95% CI for the percentage is > 91%.

The historical and expected SVR_{12} rates for the third primary endpoint of the current study align with those from the Global Phase 3 Study M15-464. To align with the non-inferiority margin used in the Global studies, a non-inferiority margin of 6% was

chosen for this study. Therefore, the percentage of subjects with SVR_{12} will be non-inferior to the historical SVR_{12} rate of 95% if the lower confidence bound of the 2-sided 95% CI for the percentage is > 89%.

Table 3. SVR_{12} Rates for Calculation of Historical and Expected SVR_{12} Rates

	GT1	GT2	GT3	GT4 – 6	Overall
Historical SVR_{12}	97%	95%	98%	95%[a]	96%
Expected ABT-493/ABT-530 SVR_{12}	97%	96%	97%	95%[a]	97%
Weight	51%	37%	7%	5%	--

GT = genotype; SVR_{12} = sustained virologic response 12 weeks postdosing

a. Global Study M13-583 did not provide estimates of these rates; 95% was chosen as a conservative estimate.

4.4 Planned Analyses

The primary analysis will occur after all subjects in Arm A have completed the PT Week 12 Visit or prematurely discontinued the study. The primary analysis will summarize data through PT Week 12 for Arm A subjects and data through the DB Treatment Period for Arm B subjects. The data for the primary analysis will be locked after data cleaning, and data collected after this lock will be added to a new version of the database. Results from the primary analysis will be described in the primary clinical study report (CSR) and submitted to regulatory agencies as part of an NDA submission.

An interim analysis will occur after all Arm A subjects have completed the PT Week 24 Visit or prematurely discontinued the study and all Arm B subjects have completed the PT Week 12 Visit or prematurely discontinued the study. The data for the interim analysis will be locked after data cleaning, and data collected after this lock will be added to a new version of the database.

The final analysis will be conducted after all subjects enrolled in the study have completed the PT Week 24 Visit or prematurely discontinued the study. The data for the final analysis will be cleaned and locked at the end of the study and included in the final CSR.

All analyses will be conducted by statisticians and programmers at AbbVie (or their designees) according to the methodologies specified in this SAP. There is no intention of shortening the follow-up time of subjects based on efficacy findings from the primary or interim analyses. All subjects who receive active study drug will be followed for 24 weeks following treatment. Therefore, no statistical adjustment will be employed due to the primary or interim analysis.

5.0 Analysis Populations

5.1 Definitions of Analysis Populations

Within each of the populations defined below, subjects who are GT1-infected and GT2-infected will be categorized as such. The categorization of these 2 groups will be based on the latest determination of genotype from the baseline sample (by the central laboratory or by phylogenetic analysis, with preference given to the phylogenetic analysis results) at the time of the primary SVR_{12} analysis.

5.1.1 Intention-to-Treat (ITT) Population

All randomized subjects who receive at least one dose of study drug in the DB Treatment Period will be included in the ITT population. The data from the ITT population will be presented by the treatment arm assigned at the time of randomization (Arm A or Arm B).

Efficacy analyses and analyses of compliance data will be performed on the ITT population, unless otherwise specified. If the ITT population differs from the safety population (as described in Section 5.1.3), analyses of demographics and baseline characteristics will also be performed on the ITT population by treatment arm.

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 have multiple GTs according to the central laboratory or phylogenetic analyses of the baseline sample or subjects who received an incorrect duration of treatment due to incorrect classification of

GT or treatment experience at randomization (mITT-GT), and on the mITT-GT population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (i.e., subjects with reasons other than on-treatment HCV virologic failure and relapse) (mITT-GT-VF).

5.1.3 Safety Population

All subjects who receive at least one dose of study drug in the DB Treatment Period will be included in the safety population. Analyses of safety; demographics; baseline characteristics; medical history; prior, concomitant, and post-treatment medications; and study drug exposure will be performed on the safety population according to actual treatment received during the DB Treatment Period even if this differs from the randomized treatment assignment; i.e., subject grouping will be based on the actual treatment received, not the arm to which the subject was randomized. If all subjects take the treatment to which they were randomly assigned, the safety population will be presented in the same way as the ITT population.

5.1.4 Open-Label (OL) Population

All subjects randomized to Arm B who receive at least one dose of active, OL study drug during the OL Treatment Period will be included in the OL population. All analyses of data collected for subjects in Arm B during and after the OL Treatment Period will be performed on the OL population.

5.2 Variables Used for Stratification of Randomization

Randomization of subjects will be stratified by geographic region (China, Singapore and South Korea), genotype (GT1, GT2, combined GT3 – 6), and HCV/HIV co-infection status (yes, no).

If a subject was randomized based on incorrect stratification information, the correct stratification information (if known at the time of the primary SVR_{12} analysis) will be used to define subpopulations for analyses.

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 (other than intensive PK samples) are to be performed prior to administering the first dose of study drug. Therefore, all Day 1 assessments for which time is not collected will be assumed to be pre-dose and the baseline value will be the last non-missing measurement collected on or before the first day of study drug administration.

All Day 1 assessments with time available must be before the time of first dose to be considered baseline, and the last non-missing measurement collected before the date and time of the first dose of study drug will be considered the baseline value. Only for resistance analyses, the last sample collected before OL Day 1 will be considered the baseline value for Arm B subjects. 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 PT 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

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

DB study days are calculated for each time point in the DB Treatment Period relative to the first dose of DB (active or placebo) study drug. Study days are negative values when the time point of interest is prior to the first DB study drug dose day. Study days are positive values when the time point of interest is after the first DB study drug dose day.

There is no DB Study Day 0. DB Study Day 1 is the day of the first dose of DB study drug in the DB Treatment Period.

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

Study drug end days are calculated for each time point relative to the last dose of DB study drug. The last day of DB study drug dosing is defined as DB Study Drug End Day 0. Days before it have negative study drug end days and days after it have positive study drug end days.

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

Active Study Days will be defined for all subjects who receive at least one dose of ABT-493/ABT-530 (DB or OL) study drug.

Active Study Day 1 is the day of the first dose of active study drug. For subjects randomized to Arm A, DB Study Days and Active Study Days are equivalent. For subjects randomized to placebo (Arm B) and in the OL population, Active Study Days are based on the first dose of OL active study drug.

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

Active study drug end days are calculated for each time point relative to the last dose of ABT-493/ABT-530 (DB or OL) study drug. The last day of active study drug dosing is defined as Active Study Drug End Day 0. Days before it have negative study drug end days and days after it have positive study drug end days.

For subjects randomized to Arm A, DB Study Drug End Days and Active Study Drug End Days are equivalent. For subjects randomized to placebo (Arm B) and in the OL population, Active Study Drug End Days are based on the last dose of OL active study drug.

Final Treatment Value

The final treatment value is defined as the last non-missing measurement collected after Study Day 1 dosing time within a treatment period as defined below.

During the DB Treatment Period, the Final DB Treatment Value is defined separately for placebo and active subjects. Subjects randomized to placebo (Arm B) should take the first dose of OL study drugs the day immediately after the last day of the DB Treatment Period. Therefore, for Arm B subjects, the Final DB Treatment Value is defined as the last non-missing measurement collected after DB Study Day 1 and no more than 2 days after the last dose of placebo and before OL Day 1 (if applicable). For subjects randomized to active study drug (Arm A), the Final DB Treatment Value is defined as the last non-missing measurement collected after DB Study Day 1 and within 2 days of the last dose of active study drug (i.e., on or before Active Study Drug End Day 2).

During the OL Treatment Period, for subjects randomized to placebo who receive OL study drug, the Final OL Treatment Value is defined as the last non-missing measurement collected after OL Day 1 and on or before Active Study Drug End Day 2.

Final Post-Treatment Value

The final PT value for each subject is the last non-missing measurement collected after Active Study Drug End Day 2 and on or before Active 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, Table 5 and Table 6 describe how efficacy data are assigned to protocol-specified time points during the DB Treatment, OL Treatment, and PT Periods, respectively. All time points and corresponding time windows are defined based on the date/time of blood sample collection.

For safety laboratory data, vital signs, and PRO instruments, the time windows specified in Table 4, Table 5 and Table 7 describe how data are assigned to protocol-specified time points.

For samples of plasma HIV-1 RNA 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 8, Table 9, and Table 10 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 (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, a vital sign parameter, or a flow cytometry 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 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 PRO Instruments (DB Treatment Period)

Scheduled Visit	Nominal Day (DB Study Day)	Time Window (DB Study Day Range)
DB Day 1/Baseline[a]	1[a]	≤ 1[a]
DB Week 1	7	2 to 10
DB Week 2	14	11 to 21
DB Week 4	28	22 to 42
DB Week 8	56	43 to 70
DB Week 12[b]	84	71 to 98
DB Week 16[b]	112	99 to 126
Final DB Treatment Visit[c]	2 to ≤ 2 days after last dose of DB study drug	

a. Day of first dose of DB study drug.

b. For 16-week treatment only.

c. The last value within the window will be used to define the Final DB Treatment Visit value. For Arm A subjects, the upper bound of this Final window is DB Study Drug End Day 2. For Arm B subjects, it is the earlier of DB Study Drug End Day 2 and the day of first dose of OL active study drug. DB Study Drug End Day 0 is defined as the day of the last dose of DB study drug.

Note: For all windows, data must be on or before DB Study Drug End Day 2, and for Arm B subjects data must also be on or before the day of first dose of OL active study drug. The result closest to the scheduled time point will be used. PRO instruments are collected at DB Day 1, DB Week 4, DB Week 12 (if 16-week treatment), and DB End of Treatment Visit.

Table 5. Analysis Time Windows for HCV RNA and Resistance Endpoints and Safety Laboratory and Vital Sign Measurements (OL Treatment Period)

Scheduled Visit[a]	Nominal Day (Active Study Day)	Time Window (Active Study Day Range)
OL Day 1[b]	1	
OL Week 1	7	2 to 10
OL Week 2	14	11 to 21
OL Week 4	28	22 to 42
OL Week 8	56	43 to 70
OL Week 12[c]	84	71 to 98
OL Week 16[c]	112	99 to 126
Final OL Treatment Visit[d]	2 to ≤ 2 days after last dose of OL study drug	

a. OL visits are applicable for subjects randomized to Arm B (placebo) who received at least one dose of OL active study drug.

b. Day of first dose of OL active study drug. For resistance analyses only, baseline value for Arm B subjects will use the last sample collected before OL Day 1.

c. For 16-week treatment only.

d. The last value within the window will be used to define the Final OL Treatment Visit value. The upper bound of this Final window is Active Study Drug End Day 2. Active Study Drug End Day 0 is defined as the day of the last dose of active study drug.

Note: For all windows, data must be on or before Active Study Drug End Day 2. The result closest to the scheduled time point will be used. PRO instruments are not collected for Arm B subjects during the OL Treatment Period.

Analyses of these data will not be included in the primary CSR.

Table 6. Analysis Time Windows for HCV RNA and Resistance Endpoints (Post-Treatment Period)

Scheduled Visit[a]	Nominal Day (Active Study Drug End Day)	Time Window (Active 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[b]	168	127 to 999
SVR_4[c]	28	3 to 56
SVR_{12}[c]	84	57 to 126
SVR_{24}[b,c]	168	127 to 210

a. PT Visits are applicable for subjects who received at least one dose of active (DB or OL) study drug.

b. Not included in primary CSR; for Arm B, included only in final CSR.

c. 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 Active Study Drug End Day 2. Active Study Drug End Day 0 is defined as the day of the last dose of active study drug.

Analyses of these data for Arm B will not be included in the primary CSR.

Table 7. Analysis Time Windows for Safety Laboratory and Vital Sign Measurements and PRO Instruments (Post-Treatment Period)

Scheduled Visit[a]	Nominal Day (Active Study Drug End Day)	Time Window (Active 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[b]	168	127 to 999
Final Post-Treatment Visit[c]	> 2 days after last dose of active study drug	

a. PT Visits are applicable for subjects who received at least one dose of active (DB or OL) study drug.

b. Not included in primary CSR; for Arm B, included only in final CSR.

c. The last value within the PT Period window will be used to define the Final PT Visit value. The lower bound of this Final window is Active Study Drug End Day 3. Active Study Drug End Day 0 is defined as the day of the last dose of active study drug.

Note: The result closest to the scheduled time point will be used. For all windows, data must occur after Active Study Drug End Day 2. Vital signs are collected at every PT visit; hematology, chemistry, urinalysis, and coagulation panels are collected at PT Week 4 or PT D/C (if subject discontinued prior to PT Week 4); PRO instruments are collected for Arm A subjects only and only at PT Week 12 and PT Week 24 (or PT D/C).

Analyses of these data for Arm B will not be included in the primary CSR.

Table 8. Analysis Time Windows for HIV-1 RNA and Flow Cytometry Measurements (DB Treatment Period)

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

a. Day of first dose of DB study drug.

b. For 16-week treatment only.

c. The last value within the window will be used to define the Final DB Treatment Visit value. For Arm A subjects, the upper bound of this Final window is DB Study Drug End Day 2. For Arm B subjects, it is the earlier of DB Study Drug End Day 2 and the day of first dose of OL active study drug. DB Study Drug End Day 0 is defined as the day of the last dose of DB study drug.

Note: Time windows specified in this table are for HCV/HIV co-infected subjects only. For all windows, data must be on or before DB Study Drug End Day 2, and for Arm B subjects, data must also be on or before the day of first dose of OL active study drug. The result closest to the scheduled time point will be used. Flow cytometry samples are collected at DB Day 1, DB Week 4, DB Week 12 (if 16-week treatment), and DB End of Treatment Visit.

Table 9. Analysis Time Windows for HIV-1 RNA and Flow Cytometry Measurements (OL Treatment Period)

Scheduled Visit[a]	Nominal Day (Active Study Day)	Time Window (Active Study Day Range)
OL Week 1	7	2 to 10
OL Week 2	14	11 to 21
OL Week 4	28	22 to 42
OL Week 8	56	43 to 70
OL Week 12[b]	84	71 to 98
OL Week 16[b]	112	99 to 126
Final OL Treatment Visit[c]	2 to ≤ 2 days after last dose of OL study drug	

a. OL visits are applicable for subjects randomized to Arm B (placebo) who received at least one dose of OL active study drug.

b. For 16-week treatment only.

Table 9. Analysis Time Windows for HIV-1 RNA and Flow Cytometry Measurements (OL Treatment Period) (Continued)

c. The last value within the window will be used to define the Final OL Treatment Visit value. The upper bound of this Final window is Active Study Drug End Day 2. Active Study Drug End Day 0 is defined as the day of the last dose of active study drug.

Note: Time windows specified in this table are for HCV/HIV co-infected subjects only. For all windows, data must be on or before Active Study Drug End Day 2. The result closest to the scheduled time point will be used. Flow cytometry samples are collected at OL Week 4, OL Week 12 (if 16-week treatment), and OL End of Treatment Visit.

Analyses of these data will not be included in the primary CSR.

Table 10. Analysis Time Windows for HIV-1 RNA and Flow Cytometry Measurements (Post-Treatment Period)

Scheduled Visit[a]	Nominal Day (Active Study Drug End Day)	Time Window (Active 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[b]	168	127 to 999
Final Post-Treatment Visit[c]	> 2 days after last dose of active study drug	

a. PT Visits are applicable for subjects who received at least one dose of active (DB or OL) study drug.

b. Not included in primary CSR; for Arm B, included only in final CSR.

c. The last value within the PT Period window will be used to define the Final PT Visit value. The lower bound of this Final window is Active Study Drug End Day 3. Active Study Drug End Day 0 is defined as the day of the last dose of active study drug.

Note: Time windows specified in this table are for HCV/HIV co-infected subjects only. The result closest to the scheduled time point will be used. For all windows, data must occur after Active Study Drug End Day 2.

Analyses of these data for Arm B will not be included in the primary CSR.

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. A subject 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 PT relapse and on-treatment virologic failure.

Missing Data Imputation for PRO Questionnaires

The handling of missing data for patient reported outcomes (PROs) will be as follows. The missing items of the FSS questionnaire will be imputed with the average score of the answered items as long as more than 50% of the items on the FSS are answered. For EQ-5D-3L index and VAS scores, no imputation will be performed for missing items.

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

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

The safety population (and ITT population if it differs from the safety population) will be used to summarize demographics and baseline characteristics by treatment arm (Arm A and Arm B) and across the treatment arms for the set of all subjects, for each of the GT1-infected and GT2-infected groups, and for the geographic region of China during the DB Treatment Period. In addition, demographics and baseline characteristics will be summarized for the geographic region of China for each of the GT1-infected and GT2-infected groups.

The safety population will be used to summarize medical history and previous, concomitant, and PT medications by treatment arm and across the treatment arms for the set of all subjects and for the geographic region of China.

7.1 Demographic and Baseline Characteristics

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

Continuous demographic variables include age, weight, height, waist circumference, and body mass index (BMI). Categorical demographic variables include sex, age category (< 65 or ≥ 65 years; < 75 or ≥ 75 years), BMI category (< 25, ≥ 25 to < 30, or ≥ 30 kg/m^2), race, ethnicity, type of Asian descent (Chinese, Korean, Malay or Other), and geographic region.

Continuous baseline characteristics include baseline $\log_{10}$ HCV RNA level, homeostasis model of assessment – insulin resistance (HOMA-IR), platelet count, albumin, GGT, LDL, HDL, total insulin, APRI, FIB-4, AST, ALT, AST/ALT ratio, creatinine clearance

(by Cockcroft-Gault formula, defined below), eGFR (using the modification of diet in renal disease [MDRD] formula modified for the Chinese population [C-MDRD], defined below), total, direct, and indirect bilirubin, total international normalized ratio (INR).

Categorical baseline characteristics include:

- HCV genotype (1, 2, 3, 4, 5, or 6) and available subtype (as determined by the central laboratory);
- HCV genotype (1, 2, 3, 4, 5, or 6) and available subtype (final HCV genotype and subtype as defined in Section 10.8);
- Prior HCV treatment history (naïve or experienced);
- HCV genotype (1, 2, 3, 4, 5, or 6) (as determined by the central laboratory) and prior HCV treatment history;
- HCV genotype (final HCV genotype as defined in Section 10.8) and prior HCV treatment history;
- For treatment-experienced subjects, type of prior treatment experience (IFN-based or SOF-based; subjects who received SOF will be categorized as SOF-based);
- For treatment-experienced subjects, type of non-response to previous treatment (on-treatment nonresponder or breakthrough, post-treatment relapse, or unknown/other);
- Screening HIV co-infection status (HCV mono-infected or HCV/HIV co-infected);
- IL28B genotype (CC, CT, or TT; CC or non-CC);
- Baseline HCV RNA level (< 1,000,000 or ≥ 1,000,000 IU/mL; < 6,000,000 or ≥ 6,000,000 IU/mL; < 10,000,000 or ≥ 10,000,000 IU/mL);
- Baseline HOMA-IR (< 2 or ≥ 2 mU × mmol/L^2);
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, F4 [if applicable]);
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);

- Baseline creatinine clearance (Cockcroft-Gault) (< 60, ≥ 60 to < 90, or ≥ 90 mL/min);
- Baseline eGFR (C-MDRD) (< 60, ≥ 60 to < 90, or ≥ 90 mL/min/1.73 m^2);
- Baseline total bilirubin (< 34.2 or ≥ 34.2 umol/L);
- Baseline total INR (continuous and < 1.7 or ≥ 1.7);
- History of diabetes (yes/no);
- History of bleeding disorders (yes/no);
- History of depression or bipolar disorder (yes/no);
- History of cardiovascular disease (yes/no);
- Baseline metabolic syndrome (yes/no);
- Injection drug use (yes, within last 12 months; yes, more than 12 months ago; or no);
- Baseline stable opiate substitution use (yes/no);
- Baseline hepato-protectant medication use (as determined by investigator on concomitant medication eCRF, yes/no);
- Tobacco use (user, ex-user, or non-user);
- Alcohol use (drinker, ex-drinker, or non-drinker);
- Concomitant use of Proton Pump Inhibitors (PPIs) (yes/no).

The demographic and baseline characteristics specified above, along with the following, will be summarized for subjects with HCV/HIV co-infection at Screening for the overall safety population and for the geographic region of China:

- HIV-1 treatment status (antiretroviral therapy [ART]-Naïve, ART-Treated),
- HIV-1 ART regimen (e.g., raltegravir [RAL], dolutegravir [DTG], rilpivirine [RPV]) for those receiving ART (as determined by investigator on concomitant medication eCRF) at baseline,
- Baseline CD4+ T-cell count (continuous; and < 200, 200 to < 350, 350 to < 500, or ≥ 500 cells/mm^3).

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

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

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

Baseline fibrosis stage is defined for subjects with non-missing liver biopsy scores, FibroScan scores, or FibroTest scores. Only one score will be used to categorize each subject even if a subject has more than one score recorded. If a biopsy score is present, then it will be used to categorize the subject, regardless of the FibroScan/FibroTest score. Similarly, if a FibroScan score is present along with a FibroTest score, then the FibroScan score will be used to categorize the subject. If biopsy and FibroScan scores are not present and more than one FibroTest result is available, then the baseline FibroTest result (i.e., last non-missing FibroTest result on or before DB Day 1) will be used to categorize the subject. Subjects will be categorized as F0 – F1, F2, F3 or F4 according to Table 11.

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

Table 11. Baseline Fibrosis Stage

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

Baseline APRI and FIB-4 are calculated by 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.

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

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

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

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

The central laboratory calculates eGFR by C-MDRD using the following equation, where serum creatinine is measured in mg/dL and age is measured in years:

> eGFR (mL/min/1.73 m^2) = 175 × (Serum Creatinine)$^{-1.234}$ × (Age)$^{-0.179}$ × (0.79 if female).

Subjects will be classified as having metabolic syndrome if at least 3 of the 5 characteristics in Table 12 are present.

Table 12. Clinical Identification of Metabolic Syndrome

Risk Factor	Defining Level in Conventional Units	Defining Level in SI Units
Abdominal obesity, given as waist circumference		
Men	> 40 in	> 102 cm
Women	> 35 in	> 88 cm
Triglycerides	≥ 150 mg/dL	≥ 1.695 mmol/L
HDL cholesterol		
Men	< 40 mg/dL	< 1.03452 mmol/L
Women	< 50 mg/dL	< 1.29315 mmol/L
Blood pressure (BP)	Systolic BP ≥ 130 mm Hg or Diastolic BP ≥ 85 mm Hg	
Fasting glucose	≥ 100 mg/dL	≥ 5.5507 mmol/L

Cross reference: Grundy 2004[6]

Medical history data 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. Histories of diabetes, bleeding disorders, depression or bipolar disorder, and cardiovascular disease will be defined by a subject having medical history coded to at least 1 preferred term within any of the high level terms specified for the category in Table 13.

Table 13. Medical History Categories

Category	MedDRA High Level Term Name
Diabetes	Diabetic complications cardiovascular Diabetic complications dermal Diabetic complications gastrointestinal Diabetic complications NEC Diabetic complications neurological Diabetic complications ophthalmic Diabetic complications renal Diabetes mellitus (incl subtypes) Hyperglycaemic conditions NEC
Bleeding disorders	Coagulation factor deficiencies Coagulopathies Platelet disorders NEC Thrombocytopenias Coagulation disorders congenital
Depression or bipolar disorder	Depressive disorders Bipolar disorders Mood alterations with manic symptoms

Table 13. Medical History Categories (Continued)

Category	MedDRA High Level Term Name
Cardiovascular disease	Coronary artery disorders NEC
	Ischaemic coronary artery disorders
	Cardiac conduction disorders
	Rate and rhythm disorders NEC
	Supraventricular arrhythmias
	Ventricular arrhythmias and cardiac arrest
	Congenital cardiac malpositions and transpositions
	Congenital cardiac structural defects NEC
	Congenital cardiovascular disorders NEC
	Cardiac disorders congenital NEC
	Cardiac hypoplasias congenital
	Cardiac malpositions congenital
	Cardiac septal defects congenital
	Cardiac valve disorders congenital
	Cardiovascular disorders congenital NEC
	Great vessel disorders congenital
	Multiple cardiac abnormalities congenital
	Persistent foetal circulation disorders
	Heart failure signs and symptoms
	Heart failures NEC
	Left ventricular failures
	Right ventricular failures
	Accelerated and malignant hypertension
	Renal hypertensions
	Vascular hypertensive disorders NEC
	Coronary necrosis and vascular insufficiency
	Infectious myocarditis
	Noninfectious myocarditis
	Peripheral vasoconstriction, necrosis and vascular insufficiency
	Aortic valvular disorders
	Cardiac valve disorders NEC
	Mitral valvular disorders
	Pulmonary valvular disorders
	Tricuspid valvular disorders
	Aortic inflammatory disorders
	Arterial inflammations
	Vasculitides NEC

7.2 Medical History

Medical history data will be coded using the MedDRA coding dictionary; the actual version of the MedDRA coding dictionary will be noted in the clinical study report. Medical history data will be summarized and presented using MedDRA System Organ Class (SOC) and preferred term. The SOCs will be presented in alphabetical order, and the preferred term will be presented in alphabetical order within each SOC. The number and percentage of subjects with a particular preferred term will be summarized for each treatment arm. Subjects reporting more than one preferred term within each SOC will be counted only once for that SOC.

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

Hepatoprotective medications taken at baseline will be summarized by generic drug name for each treatment arm.

Prior medications will be divided into the following categories:

- Prior HCV medications taken by treatment-experienced subjects;
- Prior HIV medications taken by HCV/HIV co-infected subjects receiving ART (as determined by investigator on concomitant medication eCRF) at baseline;
- All other prior medications for all treated subjects.

Concomitant medications will be divided into the following categories:

- Concomitant HIV medications taken by HCV/HIV co-infected subjects;
- All other concomitant medications for all treated subjects.

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

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 and for subjects who screen failed within each geographic region (China, Singapore and South Korea).

8.1 Disposition of Safety Population

The number of subjects in each of the following categories will be summarized by investigator and across investigators for each treatment arm and across treatment arms for the set of all subjects and for the GT1-infected and GT2-infected groups; within these 3 groups of subjects, summaries will also be performed for each geographic region (China, Singapore and South Korea):

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

- Subjects ongoing in the Post-Treatment Period (if applicable at the time of analysis).

Note that subjects randomized to placebo may prematurely discontinue DB study drug but upon unblinding at the DB Premature Discontinuation visit find that they are on placebo and elect to continue to attend all remaining DB Treatment Period study visits in order to receive OL, active study drug in the OL Treatment Period. For these placebo subjects, reasons for discontinuation from DB study drug will be collected on the DB Study Drug Completion eCRF. If such a placebo subject chooses to continue the DB Treatment Period in order to enter the OL Treatment Period, but then prematurely discontinues from the DB Period, they will be discontinued from the study entirely.

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

The number and percentage of subjects with reported study drug interruptions will be summarized by treatment arm and overall during the DB and OL Treatment Periods for the set of all subjects and for the geographic region of China.

Reasons for study drug interruptions will be presented in the CSR listings.

9.0 Study Drug Exposure and Compliance

The summaries described below will be performed for the set of all subjects and for the geographic region of China.

9.1 Exposure

The duration of exposure to study drug will be summarized separately for the DB Treatment Period (for each treatment arm and overall in the safety population) and the OL Treatment Period (for the OL population). For each of the treatment periods, duration of

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

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for exposure during each treatment period. Study drug duration will also 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 during the DB Treatment Period (for each treatment arm and overall in the safety population) and the OL Treatment Period (for the OL population) with a study drug duration of ≥ 52 days or ≥ 105 days will be summarized.

9.2 Compliance

During the DB and OL Treatment Periods, at each Study Drug Dispensation visit the number of tablets dispensed is automatically calculated according to the number of bottles dispensed, and at each Study Drug Accountability visit (starting with the Week 4 visit), the total number of tablets returned is recorded. The compliance for each study drug (ABT-493/ABT-530 or matching placebo) during the DB Treatment Period will be calculated as the percentage of tablets taken relative to the total tablets expected to be taken. The total number of tablets expected to be taken will be equal to the total number of tablets that should have been taken per the protocol for the duration that the subject was in the DB Treatment Period (date of last dose of study drug – date of first dose of study

drug + 1). DB study drug interruptions recorded on the eCRF will not be subtracted from the duration.

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

The summaries described above will be performed on the ITT population; similar summaries of the compliance for the active study drug (ABT-493/ABT-530) during the OL Treatment Period will be provided for the OL population.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

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

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

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

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

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

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

Definitions for Efficacy Endpoints

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 HCV 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 active 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 active 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 active study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

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

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

$Relapse_{overall}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the PT Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment and has post treatment HCV RNA data available, excluding reinfection.

Only subjects who have at least one post-treatment HCV RNA value will be included in analyses of relapse. For the analyses of relapse, completion of treatment is defined as a study drug duration of 52 days or greater for subjects assigned to 8 weeks of treatment and 105 days or greater for subjects assigned to 16 weeks of treatment. 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 active treatment in a subject who had HCV RNA < LLOQ at Final Treatment Visit, along with the post treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis of the NS3 or NS5A, and/or NS5B gene sequences. Reinfection in the case of the same HCV subtype is defined as a clade switch, as indicated by the lack of clustering between the baseline and post-treatment sequences by phylogenetic analysis. If phylogenetic analysis is not possible due to technical difficulties, HCV reinfection may be determined with a confirmed HCV genotype or subgenotype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Post-treatment relapse is defined as described earlier (**$Relapse_{12}$, $Relapse_{24}$, $Relapse_{overall}$**), and no genotype, subtype, or clade switch compared with baseline as determined by phylogenetic analysis of the NS3 or NS5A gene sequences. If phylogenetic analysis is not possible due to technical difficulties, the subject will be defined as having a post-treatment relapse unless an HCV genotype or subgenotype switch is confirmed by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Reasons for SVR_{12} Non-Response

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

1. On-treatment HCV virologic failure (see **On-treatment HCV virologic failure** definition; if a subject meets both definitions of **Breakthrough** and **EOT failure**, he or she will be categorized as **Breakthrough** only);
2. $Relapse_{12}$;
3. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR_{12} non-responder who prematurely discontinued study drug [study drug duration < 52 days for subjects assigned to 8 weeks of treatment, and

< 105 days for subjects assigned to 16 weeks of treatment] and did not meet the **On-treatment HCV virologic failure** definition);

4. HCV reinfection (see definition described earlier);
5. Missing follow-up data in the SVR_{12} window (defined as any subject who completed study drug without data in the SVR_{12} window after applying the imputation rules and not meeting the definitions of [1], [2], [3], or [4]);
6. Other (defined as any SVR_{12} non-responder not meeting the definitions of [1] – [5]).

Reasons for SVR_{24} Non-Response

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

1. On-treatment HCV virologic failure (see **On-treatment HCV virologic failure** definition, if a subject meets both definitions of **Breakthrough** and **EOT failure**, he or she will be categorized as **Breakthrough** only);
2. $Relapse_{12}$;
3. $Relapse_{24}$;
4. Prematurely discontinued study drug with no on-treatment virologic failure and no relapse after achieving SVR_{12} (defined as any SVR_{24} non-responder who prematurely discontinued study drug [study drug duration < 52 days for subjects assigned to 8 weeks of treatment, and < 105 days for subjects assigned to 16 weeks of treatment] and did not meet the **On-treatment HCV virologic failure or $Relapse_{24}$** definitions);
5. HCV reinfection (see definition described earlier);

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 1 category. For example, the categories of premature discontinuation and reinfection are mutually exclusive. Thus, subjects who are SVR_{12} or SVR_{24} nonresponders meeting the definition of HCV reinfection will be counted in the reinfection category and will not be counted in any other category (as in the example, even if such a subject appears to meet the definition of prematurely discontinued study drug with no on-treatment HCV virologic failure, the subject would be counted in the reinfection category only).

10.2 Handling of Multiplicity

In order to control the Type I error rate at 0.05, a fixed sequence testing procedure[7] will be used for the ranked primary efficacy endpoints. That is, only if success has been demonstrated for the first primary endpoint will the testing proceed to the second primary endpoint. Similarly, only if success has been demonstrated for the second primary endpoint will the testing proceed to the third primary endpoint.

10.3 Primary Efficacy Analysis

The primary efficacy endpoint is the percentage of Arm A subjects achieving SVR_{12}. The three ranked primary efficacy endpoints are:

1. The percentage of Arm A subjects from the combined group of GT1 to 6-infected subjects in the ITT population achieving SVR_{12}. The percentage of these subjects with SVR_{12} will be non-inferior to the historical SVR_{12} rate of 96% if the lower confidence bound (LCB) of the 2-sided 95% CI for the percentage is > 90%.

2. The percentage of Arm A subjects from the group of GT1-infected subjects in the ITT population achieving SVR_{12}. The percentage of these subjects with SVR_{12} will be non-inferior to the historical SVR_{12} rate of 97% if the LCB of the 2-sided 95% CI for the percentage is > 91%.

3. The percentage of Arm A subjects from the group of GT2-infected subjects in the ITT population achieving SVR_{12}. The percentage of these subjects with SVR_{12} will be non-inferior to the historical SVR_{12} rate of 95% if the LCB of the 2-sided 95% CI for the percentage is > 89%.

   The normal approximation to the binomial distribution will be used to calculate each CI unless the rate for the primary endpoint is 100%, in which case the Wilson's score method will be used for the calculation of the CI.[8]

10.4 Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- the percentage of Arm A subjects with on-treatment HCV virologic failure (defined as **On-treatment HCV virologic failure**);
- the percentage of Arm A subjects with post-treatment relapse (defined as **$Relapse_{12}$**; subjects with reinfection will be summarized separately);
- the percentage of Arm A HCV/HIV co-infected subjects (determined at Screening) achieving SVR_{12}.

The numbers and percentages of subjects with on-treatment HCV virologic failure, post-treatment relapse (**$Relapse_{12}$**), and SVR_{12} will be calculated along with two-sided 95% Wilson score CIs.[8]

In addition, a summary of reason for SVR_{12} non-response (e.g., on-treatment HCV virologic failure, relapse, re-infection, other) will be provided for the set of all Arm A subjects and for the set of HCV/HIV co-infected Arm A subjects. Listings of subject numbers with reason for non-response will be prepared.

The secondary endpoints will be summarized for the set of all Arm A subjects in the ITT population and for the Arm A subjects in each of the GT1-infected and GT2-infected groups.

10.5 Sensitivity Analyses for SVR_{12}

Two-sided 95% CIs for the SVR_{12} rates of the primary endpoints will be calculated using both the normal approximation to the binomial distribution and the Wilson score method.[8]

The analyses of the primary endpoints will also be performed on Arm A of the mITT-GT and mITT-GT-VF populations. Both two-sided 95% normal approximation and Wilson score CIs will be provided for each of these sensitivity analyses.

The analyses described above will also be performed for the geographic region of China within the overall set of Arm A subjects and the Arm A subjects in each of the GT1-infected and GT2-infected groups for the populations specified above.

The number and percentage of subjects with SVR_{12} and the corresponding 95% Wilson score CI will be provided for each randomization stratum:

- China/GT1-infected/HIV co-infected
- China/GT1-infected/non-HIV co-infected
- China/GT2-infected/HIV co-infected
- China/GT2-infected/non-HIV co-infected
- China/GT3 – 6-infected/HIV co-infected
- China/GT3 – 6-infected/non-HIV co-infected
- Singapore/GT1-infected/HIV co-infected
- Singapore/GT1-infected/non-HIV co-infected
- Singapore/GT2-infected/HIV co-infected
- Singapore/GT2-infected/non-HIV co-infected
- South Korea/GT1-infected/HIV co-infected
- South Korea/GT1-infected/non-HIV co-infected

- South Korea/GT2-infected/HIV co-infected
- South Korea/GT2-infected/non-HIV co-infected

For each sensitivity analysis, a two-sided 95% CI will be produced only if there are at least 10 subjects in the summary.

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

10.5.1 Imputation Approaches

In addition to imputing SVR_{12} as described in Section 6.3, SVR_{12} will be presented for the overall set of Arm A subjects and the Arm A subjects in each of the GT1-infected and GT2-infected groups in the ITT population using the following other methods to impute missing HCV RNA values:

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

For each of these, the number and percentage of Arm A subjects with SVR_{12} will be presented along with two-sided 95% CIs using both the normal approximation to the binomial distribution and the Wilson score method. Within the 3 groups of subjects specified above, these analyses will also be performed for the geographic region of China.

10.5.2 Assessment of Homogeneity Across Stratification Variables

Heterogeneity across the randomization stratification variables of geographic region, genotype, and HCV/HIV co-infection status will be examined for the primary efficacy

endpoint of SVR_{12} in Arm A using the chi-square test of homogeneity. The 14 strata are presented in Section 10.5.

If heterogeneity across the randomization stratification is detected, a confidence interval for the primary endpoint based on the 14 strata will be created using a stratum weighted variance calculated using the equations below. The variance of p_s will be estimated by:

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

and the 2-sided 95% CI will be calculated as $p_s \pm z\sqrt{Var(p_s)}$, where z is the 1-α/2 point of the standard normal distribution. Note that n represents the number of subjects in Arm A within the ITT population, n_h represents the number of subjects in stratum h, w_h *will be estimated by* n_h/n, p_h = the proportion of subjects achieving SVR_{12} in stratum h, and p_s = the proportion of subjects with SVR_{12} among n subjects which can be defined as:

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

Using the equations above, a confidence interval for the SVR_{12} rate across all 14 strata will be presented, along with the number and percentage (p_h) of subjects achieving SVR_{12} within each of the 14 strata.

10.6 Efficacy Subgroup Analysis

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

Within each subgroup, the number and percentage of Arm A subjects achieving SVR_{12} will be calculated for the set of all subjects in the ITT population and for each of the GT1-

infected and GT2-infected groups. The 2-sided 95% Wilson score CI will be produced if there are at least 10 subjects in the subgroup.

The following subgroups will be analyzed:

- HCV genotype and available subtype (based on the latest determination of genotype from the baseline sample [by the central laboratory or by phylogenetic analysis, with preference given to the phylogenetic analysis results] at the time of the primary SVR_{12} analysis);
- Prior HCV treatment history (naïve or experienced);
- For treatment-experienced subjects, type of prior treatment experience (IFN- or SOF-based);
- For treatment-experienced subjects, type of non-response to previous treatment (on-treatment nonresponder or breakthrough, post-treatment relapse, or unknown/other);
- Screening HIV co-infection status (HCV mono-infected or HCV/HIV co-infected);
- IL28B genotype (CC or non-CC);
- Sex (male or female);
- Age (< 65 or ≥ 65 years) and (< 75 or ≥ 75 years);
- Geographic region (China, Singapore, or South Korea);
- Type of Asian descent (Chinese, Korean, Malay, or Other);
- Baseline BMI (< 30 or ≥ 30 kg/m^2);
- Baseline HCV RNA level (< 1,000,000 or ≥ 1,000,000 IU/mL; < 6,000,000 or ≥ 6,000,000 IU/mL; < 10,000,000 or ≥ 10,000,000 IU/mL);
- Baseline HOMA-IR (< 2 or ≥ 2 mU × $mmol/L^2$);
- Baseline fibrosis stage (equivalent to Metavir F0 – F1, F2, F3, F4 [if applicable]);
- Baseline platelet count (< 100 or ≥ 100 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Baseline creatinine clearance (< 60, ≥ 60 to < 90, or ≥ 90 mL/min);

- Baseline eGFR (C-MDRD) (< 60, ≥ 60 to < 90, or ≥ 90 mL/min/1.73 m^2);
- History of diabetes (yes/no);
- History of bleeding disorders (yes/no);
- History of depression or bipolar disorder (yes/no);
- History of cardiovascular disease (yes/no);
- Baseline metabolic syndrome (yes/no);
- Injection drug use (yes, within last 12 months; yes, more than 12 months ago; or no);
- Baseline stable opiate substitution use (yes/no);
- Baseline hepato-protectant medication use (yes/no);
- Study drug compliance (yes/no);
- Concomitant use of PPIs (yes/no).

The summaries described above will also be performed for the geographic region of China within the overall set of Arm A subjects and the Arm A subjects in each of the GT1-infected and GT2-infected groups.

A logistic regression model will be used to explore the associations between each of the subgroup variables and SVR_{12} by fitting a logistic regression model on all subjects in the mITT-GT-VF population. Among all candidate predictors, continuous measurements will be used where possible (e.g., continuous baseline log_{10} HCV RNA level, continuous age, continuous BMI) in the logistic regression model. A stepwise logistic regression approach will be used to assess the strength of each subgroup variable in predicting SVR_{12}, with a significance level of 0.10 to enter and remain in the model.

10.7 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized for the set of all Arm A subjects in the ITT population and in each of the GT1-infected and GT2-infected groups of the ITT population; within theses 3 groups of subjects, the endpoints will also be summarized for the geographic region of China:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the DB Treatment Period (using data as observed);
- The percentage of subjects with SVR_4;
- A summary of reasons for SVR_4 non-response (e.g., on-treatment virologic failure, relapse, re-infection, other);
- The percentage of subjects with HCV virologic failure through PT Week 12 (i.e., the SVR_{12} non-responders due to on-treatment virologic failure or $Relapse_{12}$);
- The percentage of subjects with SVR_{24}*;
- A summary of reasons for SVR_{24} non-response (e.g., on-treatment virologic failure, relapse, re-infection, other)*;
- The percentage of subjects who relapsed after achieving SVR_{12} (**$Relapse_{24}$**).

* These endpoints will be summarized for the HCV/HIV co-infected subjects (determined at Screening) within the populations/groups identified above.

The following additional endpoints will be summarized for the set of all subjects in the OL Population and for each of the GT1-infected and GT2-infected groups of the OL Population; within theses 3 groups of subjects, the endpoints will also be summarized for the geographic region of China:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the OL Treatment Period (using data as observed);
- The percentage of subjects with SVR_4;
- A summary of reason for SVR_4 non-response (e.g., on-treatment virologic failure, relapse, re-infection, other);
- The percentage of subjects with SVR_{12}*;
- A summary of reason for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, re-infection, other)*;
- The percentage of subjects with SVR_{12} by HCV genotype and available subtype;

- The percentage of subjects with SVR_{12} by prior HCV treatment history (treatment-naïve and treatment-experienced, with further breakdown by type of prior HCV treatment experience);
- The percentage of subjects with SVR_{12} by geographic region;
- The percentage of subjects with HCV virologic failure through PT Week 12;
- The percentage of subjects with SVR_{24}*;
- A summary of reason for SVR_{24} non-response (e.g., on-treatment virologic failure, relapse, re-infection, other)*;
- The percentage of subjects who relapsed after achieving SVR_{12} (**$Relapse_{24}$**).

* These endpoints will be summarized for the HCV/HIV co-infected subjects (determined at Screening) within the populations/groups identified above.

In the above analyses for SVR, HCV virologic failure, and relapse, the number and percentage of subjects with each endpoint among those receiving active treatment during the DB or the OL Treatment Period, as applicable, will be calculated along with a two-sided 95% Wilson score CI. Imputations for missing data will be performed as described in Section 6.3 for analysis of SVR, HCV virologic failure, and relapse. All other endpoints will be presented using data as observed.

As additional endpoints, the secondary endpoints will be summarized for the geographic region of China within the set of Arm A subjects in the ITT population and in each of the GT1-infected and GT2-infected groups of 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 overall and by SVR visit window (within the SVR_4, SVR_{12}, SVR_{24} windows or after SVR_{24} window), including the subject number and the SVR visit window corresponding to the first HCV RNA value of those indicating the occurrence of relapse. A similar listing will be prepared for subjects who prematurely discontinued treatment and relapsed after having HCV RNA < LLOQ at their Final Treatment Visit. These summaries will be presented across geographic regions and for the geographic region of China within the set of Arm A

subjects in the ITT population and in each of the GT1-infected and GT2-infected groups of the ITT population as well as within the overall OL population and the GT1-infected and GT2-infected groups in the OL population.

Listings of subject numbers with reason for non-response will be prepared for the SVR endpoints.

The concordance between SVR_{12} and SVR_{24} will be assessed 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. These summaries will be presented across geographic regions and for the geographic region of China within the set of Arm A subjects in the ITT population and in each of the GT1-infected and GT2-infected groups of the ITT population as well as within the overall OL population and the GT1-infected and GT2-infected groups in the OL population.

For each additional analysis, a two-sided 95% CI will be produced only if there are at least 10 subjects in the summary.

10.8 HCV and HIV Resistance Analyses

For subjects who enroll in South Korea or Singapore, full length NS3/4A and NS5A from baseline samples will be sequenced by next generation sequencing (NGS). For subjects who enroll in South Korea or Singapore who experience HCV virologic failure (on-treatment HCV virologic failure or post-treatment relapse as defined in Section 10.1), full length NS3/4A and NS5A genes from the first sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by NGS. For resistance analysis only, the last

sample collected before OL Day 1 will be considered the baseline sample for Arm B subjects. For genotype 1-infected subjects experiencing virologic failure who enroll in China, amino acids 1 – 181 in NS3 and 1 – 215 in NS5A from the baseline sample and the first sample after virologic failure with HCV RNA ≥ 1000 IU/mL will be sequenced by population sequencing. An appropriate subtype-specific prototypic reference sequence will be used for comparison with sequences from samples. Subjects who experience HCV virologic failure will be referred to as subjects in the primary virologic failure (PVF) population, and a listing by subject that includes HCV subtype, IL28B genotype, reason for SVR_{12} non-response, time point(s) sequenced as closest to time of HCV virologic failure, and HCV RNA value at the HCV virologic failure time point(s) will be produced for these subjects. In addition, all listings described below will display HCV subtype, and reason for SVR_{12} non-response in the subject identifier for each subject. A separate listing will delineate all subjects in the PVF population for whom no sequencing was performed (e.g., lost to follow-up while HCV RNA ≤ 1000 IU/mL).

Subjects from South Korea and Singapore and GT1-infected subjects from China treated with active study drug who do not achieve SVR_{12} and who do not meet the above criteria for the PVF population (i.e., prematurely discontinue study drug with no on-treatment HCV virologic failure, have HCV reinfection, are missing SVR_{12} data or have other reasons as described in Section 10.1, Reasons for SVR_{12} Non-Response), but have a time point with HCV RNA ≥ 1000 IU/mL after treatment discontinuation, will have the sample at that time point sequenced. For subjects from South Korea and Singapore and GT1-infected subjects from China who are lost to follow-up with less than 6 weeks of therapy while not virally suppressed (e.g., HCV RNA never < LLOQ or have increase in viral load post-nadir), the sample at the latest available time point with HCV RNA ≥ 1000 IU/mL and the corresponding baseline sample will be sequenced. These subjects will be referred to as the non-PVF population. A listing of all subjects in the non-PVF population with post-baseline sequencing available will be created that is similar to the listing of subjects in the PVF population with post-baseline sequencing. For each DAA target, signature amino acid positions and a key subset of amino acid positions are shown

in Table 14. Appropriate subtype-specific prototypic reference sequences will be used for comparison with sequences from samples.

Table 14. List of Signature Amino Acid Positions and a 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 only)	155, 156, 168
GT1, NS5A	24, 28, 29, 30, 31, 32, 54 (GT1b only), 58, 62, 92, 93	24, 28, 30, 31, 58, 92, 93
GT2, 4 – 6, NS3	36, 43, 54, 55, 56, 80, 155, 156, 168	155, 156, 168
GT2, 4 – 6, NS5A	24, 28, 29, 30, 31, 32, 58, 62, 92, 93	24, 28, 30, 31, 58, 92, 93
GT3, NS3/4A	36, 43, 54, 55, 56, 80, 155, 156, 166, 168	155, 156, 168
GT3, NS5A	24, 28, 29, 30, 31, 32, 58, 92, and 93	24, 28, 30, 31, 58, 92, 93

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of virologic failure or treatment discontinuation is < 1000 IU/mL, the sample closest in time after failure/discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used. Included time points for analyses on 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 by population sequencing:

- Baseline polymorphism: a polymorphism in a baseline sample determined by comparison of the amino acid sequence of the baseline sample to the appropriate prototypic reference amino acid sequence for a given DAA target.

- Post-baseline substitution: an amino acid substitution in a post-baseline time point sample that was not detected at baseline in the subject.

The following definitions will be used in the resistance analyses by NGS:

- Baseline polymorphism: a polymorphism in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on frequency threshold utilized) that was not present in the appropriate prototypic reference amino acid sequence for a given DAA target (NS3/4A or NS5A).
- Substitution at signature amino acid position: substitution (relative to reference) present at a detection threshold of ≥ 2% or ≥ 15% (depending on frequency threshold utilized) within a subject's viral population in a baseline or a 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 sample.
- Enriched substitution: substitution present at both baseline and in a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post baseline % – baseline %) ≥ 20].
- Treatment-emergent substitution by NGS: a post-baseline substitution or an enriched substitution.

Analysis will be performed separately for each HCV subtype and treatment duration within each listing.

Analysis 1: The following analyses will be performed for all subjects who enroll in South Korea or Singapore:

- A listing of all baseline polymorphisms (≥ 2% detection threshold) at signature amino acid positions for each DAA target (NS3 and NS5A) for subjects in the ITT population.
- The number and percentage of subjects with baseline polymorphisms at detection-thresholds of ≥ 2% and ≥ 15% at signature amino acid positions (ITT

population). This table includes prevalence of each baseline polymorphisms and a summary of number of subjects with polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 and NS5A.

- Total number and percentage of subjects with baseline polymorphisms ***at the key subset of amino acid positions*** in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 and NS5A (ITT population) by genotype, subtype, and total.

Analysis 2: The impact of baseline polymorphisms on treatment outcome will be assessed for **mITT-GT-VF** population for subjects who enroll in South Korea or Singapore as follows: for each polymorphism, the SVR_{12} rate will be calculated for subjects with and without the polymorphisms and the 2 rates will be compared using Fisher's exact test. Analysis will be grouped by HCV subtype, treatment duration, and DAA target (NS3 or NS5A). The following will be included in the analyses of impact of baseline polymorphisms on treatment outcome:

- Polymorphisms at signature amino acid positions (vs no polymorphisms at that position), using detection thresholds of ≥ 2% and ≥ 15%. The analysis will include the number of subjects with polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A.
- Each polymorphism at signature amino acid position (vs not that variant) using detection thresholds of ≥ 2% and ≥ 15%. The analysis will include the number of subjects with polymorphisms in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 + NS5A.

Analysis 3: In subjects who enroll in South Korea or Singapore, the SVR_{12} rate will be calculated and compared using Fisher's exact test between subjects with or without polymorphisms at 15% detection threshold in NS3 only, in NS5A only, any in NS3, any in NS5A, any in NS3 or NS5A, any in NS3 and NS5A at the ***key subset of amino acid positions.*** Analysis will be performed by HCV genotype, subtype, and overall on the mITT-GT-VF population.

Analysis 4: The following analyses will be performed for subjects who enroll in South Korea or Singapore who do not achieve SVR_{12} (with separate summaries for subjects in PVF and non-PVF populations) and have post-baseline resistance data available:

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

Analysis 5: For subjects who enroll in China who experience virologic failure and have sequence data available, the following analyses will be conducted:

- A listing of all baseline polymorphisms at signature amino acid positions for each DAA target (NS3 and NS5A).
- Listings by subject of all post-baseline substitutions relative to the baseline amino acid sequence will be provided for each DAA target (NS3 and NS5A).
- Listings by subject of all emerged substitutions, by amino acid position and substitution within a DAA target in a post-baseline sample relative to the baseline amino acid sequence will be provided for each DAA target (NS3 and NS5A).
- Listings by subject of all post-baseline substitutions at signature amino acid positions relative to the appropriate prototypic reference amino acid sequence will be provided for each DAA target (NS3 and NS5A).

If resistance-associated substitutions are not detected in a given target for a subject at the time of failure/discontinuation, then that target may not be sequenced in subsequent samples from that subject.

HCV Genotype/Subtype

Phylogenetic analysis will be conducted on HCV sequence from all available baseline samples from subjects who enroll in South Korea or Singapore and genotype 1-infected

subjects experiencing virologic failure who enroll in China 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, and/or NS5A sequences performed by AbbVie. If the phylogenetic analysis is available, then it will be used to determine the subject's HCV genotype and subtype. If it is not available, then the Sanger sequencing assay result will be used to determine the subject's HCV genotype and subtype, if available. Finally, if neither the phylogenetic analysis result nor the Sanger sequencing assay results 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. The baseline characteristic summary will use the results from the central laboratory (Sanger sequencing or Inno-LiPA 2.0 Assay [if Sanger sequencing not available]).

A summary of HCV genotype 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.

HIV Drug-Resistance Analyses

If any subject on stable HIV-1 ART develops a confirmed, quantifiable plasma HIV-1 RNA level (HIV-1 RNA ≥ 200 copies/mL at one assessment and ≥ 500 copies/mL on repeat testing) after starting the study, the HIV-1 protease, reverse transcriptase and/or integrase sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays for subjects from South Korea and Singapore. The number of subjects who demonstrate HIV genotypic resistance and the genotypic resistant mutations detected in the samples obtained from these subjects will be tabulated and summarized in the final CSR, as applicable. Resistance will be defined as described by the IAS-USA Panel.[9]

10.9 Patient Reported Outcomes

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

Subject's responses to the EQ-5D-3L will be combined into a unique health state using a 5-digit code with 1 digit from each of the 5 dimensions. The EQ-5D-3L states will be converted into a single preference-weighted health utility index score by applying weights.[10,11] The VAS score will be analyzed separately. For EQ-5D-3L index and VAS scores, no imputation will be performed for missing items.

The FSS measures the impact of fatigue over the past week on specific types of functioning. The survey consists of 9 questions using a 7-point Likert scale. A total score is calculated as the average of the individual item responses (adding up all the answers and dividing by nine). Higher FSS scores indicate a higher degree of impact of fatigue. Imputation will be applied to the total score as described in Section 6.3.

Summary statistics (n and mean,) at each protocol-specified visit and for change from baseline (n, mean, SD, minimum and maximum) to each protocol-specified visit will be provided for the EQ-5D-3L health index score and VAS score and for the FSS total score for each treatment arm in the ITT population (as applicable). For each of these scores, mean change from Baseline to the final scheduled DB Treatment Period Visit (Week 8 or Week 16) will be compared between treatment arms using an analysis of covariance (ANCOVA) model with treatment arm as a factor and baseline score as a covariate.

The number and percentage of subjects who have ever experienced an increase from baseline up through each applicable time point of greater than or equal to 0.7 in the FSS total score will also be calculated for each treatment arm in the ITT population (as applicable), along with two-sided 95% CIs based on the normal approximation to the binomial distribution. In addition, percentages of subjects meeting the criteria at each applicable time point during the DB Treatment Period will be compared between Arm A and Arm B using Fisher's Exact Test.

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

The analyses described above will also be performed for the geographic region of China.

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will be performed on the safety population for data corresponding to DB treatment and on the OL population for data corresponding to OL treatment. Safety data will be summarized for the set of all subjects and for the geographic region of China.

For safety analyses, data from the active (Arm A) and placebo (Arm B) treatment arms during the DB Treatment Period will be summarized, and comparisons between Arms A and B will be performed, as appropriate. Data from the PT Period for Arm A through PT Week 4 will also be summarized for the change from baseline analyses of laboratory parameters, and through PT Week 24 for the change from baseline analyses of vital sign parameters.

Data from the OL Treatment Period and PT Period for Arm B will be not be summarized in the primary CSR, except listings of any serious adverse events and deaths from the OL Treatment Period for Arm B will be included in the primary CSR; these data will be summarized in the interim analysis (following the primary CSR) and in the final CSR.

11.2 Analysis of Adverse Events

Adverse events (AEs) will be coded using the MedDRA coding dictionary. The actual version of the MedDRA coding dictionary will be noted in the CSR.

HIV-1-infected subjects participating in clinical trials may develop infections typically associated with AIDS. A list of these known AIDS-associated opportunistic infections (OIs) is contained in Appendix D of the study protocol. AEs that are identified by the

investigators as AIDS-associated OIs will not be included in any analyses of AEs, but will be summarized separately for the HCV/HIV co-infected subjects.

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined below for the DB and OL Treatment Periods separately.

Treatment-Emergent AEs in DB Treatment Period

For the active arm (Arm A), treatment-emergent AEs are defined as any event with an onset date that is after the first dose of active study drug and no more than 30 days after the last dose of study drug. For the placebo arm (Arm B), treatment-emergent AEs are defined as any event with an onset date that is after the first dose of placebo through 30 days after the last dose of placebo and prior to OL Day 1 (if applicable). 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).

Treatment-Emergent AEs in OL Treatment Period

For subjects in the OL Population, treatment-emergent AEs are defined as any event with an onset date that is after the first dose of OL study drug and no more than 30 days after the last dose of OL study drug. Events where the onset date is the same as the OL 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 OL study drug start date).

11.2.2 Tabulations of Treatment-Emergent Adverse Events

The number and percentage of subjects with treatment-emergent AEs will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term. The SOCs will be

presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC.

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

AEs will be presented for the following 3 groups, separately: 1) DB active (Arm A during the DB Treatment period), 2) DB placebo (Arm B during the DB Treatment Period), and 3) OL active (Arm B during the OL period).

Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories; this overview will also be presented for the set of HCV/HIV co-infected subjects within the populations/groups specified in Section 11.1:

- Any treatment-emergent AE;
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (ABT-493/ABT-530);
- Treatment-emergent AEs of Grade 3 or higher;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to DAAs (ABT-493/ABT-530);
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (ABT-493/ABT-530);
- Treatment-emergent AEs leading to discontinuation of study drug;
- DAA-related treatment-emergent AEs leading to discontinuation of study drug;
- Serious treatment-emergent AEs leading to discontinuation of study drug;

- Treatment-emergent AEs leading to interruption of study drug;
- Treatment-emergent AEs leading to death;
- Deaths.

Adverse Events by SOC and Preferred Term

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

- Treatment-emergent AEs (will also be presented for the set of HCV/HIV co-infected subjects within the populations/groups specified in Section 11.1);
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (ABT-493/ABT-530);
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (ABT-493/ABT-530);
- Treatment-emergent AEs of Grade 3 or higher;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to DAAs (ABT-493/ABT-530);
- Treatment-emergent AEs leading to discontinuation of study drug;
- DAA-related treatment-emergent AEs leading to discontinuation of study drug;
- Serious treatment-emergent AEs leading to discontinuation of study drug;
- Treatment-emergent AEs leading to interruption of study drug;
- Treatment-emergent AEs leading to death.

For all treatment-emergent AEs (at the SOC and preferred term level), risk differences will be calculated for the DB active arm (Arm A) versus placebo (Arm B). The risk difference will be calculated as the percentage of subjects in Arm A with the event minus the percentage of subjects in Arm B with the event. The risk differences will be included on the summaries of AEs during the DB Treatment Period.

A listing of treatment-emergent adverse events grouped by SOC and preferred term with subject numbers will be created.

Adverse Events by Preferred Term

The following summaries of AEs tabulated according to preferred term and sorted by overall frequency in Arm A for the DB active and DB placebo groups and by frequency for the OL active group will be generated:

- Treatment-emergent AEs (will also be presented for the set of HCV/HIV co-infected subjects within the populations/groups specified in Section 11.1);
- Treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (ABT-493/ABT-530);
- Serious treatment-emergent AEs;
- Serious treatment-emergent AEs with a "reasonable possibility" of being related to DAAs (ABT-493/ABT-530);
- Treatment-emergent AEs of Grade 3 or higher;
- Treatment-emergent AEs of Grade 3 or higher with a "reasonable possibility" of being related to DAAs (ABT-493/ABT-530).

These summaries also will include the risk difference defined earlier and the 2-sided 95% CI on the risk difference using the Wilson score method for a difference in proportions.[12]

Adverse Events by Maximum Severity Grade Level

Treatment-emergent AEs and DAA-related treatment-emergent AEs will be summarized by maximum severity grade level of each preferred term. 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.

Adverse Events by Maximum Relationship

Treatment-emergent AEs also will be summarized by maximum relationship of each preferred term to study drug (DAAs), as assessed by the investigator. 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.

Adverse Events of Special Interest

The AEs of special interest include the following:

"Hepatic Decompensation and Hepatic Failure" defined by the Product MedDRA Query (PMQ);

"Hepatocellular Carcinoma" defined by the MedDRA preferred terms of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer recurrent, and hepatic cancer metastatic.

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 preferred term and across all SOCs/preferred terms. 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.

Adverse Events by HIV-1 ART Regimen

For the HCV/HIV co-infected subjects who were on HIV-1 ART at initiation of DB study drug, treatment-emergent AEs also will be summarized for the subgroups defined by the HIV-1 ART regimen (e.g., RAL, DTG, RPV) the subjects were receiving at DB study drug initiation. For each HIV-1 ART regimen, the number and percentage of subjects experiencing treatment-emergent AEs will be tabulated according to SOC and preferred term.

AIDS-Associated Opportunistic Infections

The number and percentage of subjects experiencing treatment-emergent AIDS-associated OIs will be tabulated according to SOC and preferred term for the HCV/HIV co-infected subjects (determined at Screening). Subjects reporting more than one AIDS-associated OI for a given preferred term will be counted only once for that term. Subjects reporting more than one AIDS-associated OI within a SOC will be counted only once for that SOC. Subjects reporting more than one AIDS-associated OI will be counted only once in the overall total.

11.2.3 Listings 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 death,
- Treatment-emergent AEs leading to discontinuation of study drug,
- Treatment-emergent AEs leading to study drug interruption,
- AEs (treatment-emergent or all, as applicable) in each of the AEs of special interest categories,
- Treatment-emergent AIDS-associated OIs.

11.3 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.

11.3.1 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, uric acid, cholesterol, total protein, glucose, triglycerides, albumin, chloride, bicarbonate, magnesium, total insulin, gamma-glutamyl transferase (GGT), creatinine clearance (calculated using Cockcroft-Gault), estimated glomerular filtration rate (eGFR) calculated using the modification of diet in renal disease (MDRD) equation modified for the Chinese population (C-MDRD), and creatinine phosphokinase (CPK).

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

The definitions of toxicity grades for laboratory parameters are presented in Table 15.

Table 15. 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 (high)	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L	> 27.8 mmol/L
Glucose (low)	< 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
eGFR (C-MDRD)	< LLN – 60 mL/min/1.73 m^2	< 60 – 30 mL/min/1.73 m^2	< 30 – 15 mL/min/1.73 m^2	< 15 mL/min/1.73 m^2
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	--
Lymphocyte	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L
aPTT	> ULN – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	--
Sodium (low)	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L
Sodium (high)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L	> 160 mmol/L
Potassium (low)	< LLN – 3.0 mmol/L	--	< 3.0 – 2.5 mmol/L	< 2.5 mmol/L
Potassium (high)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L	> 7.0 mmol/L

Table 15. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values (Continued)

Test	Grade 1	Grade 2	Grade 3	Grade 4
Triglycerides	> 1.71 – 3.42 mmol/L	> 3.42 – 5.7 mmol/L	> 5.7 – 11.4 mmol/L	> 11.4 mmol/L
Magnesium (low)	< LLN – 0.5 mmol/L	< 0.5 – 0.4 mmol/L	< 0.4 – 0.3 mmol/L	< 0.3 mmol/L
Magnesium (high)	> ULN – 1.23 mmol/L	--	> 1.23 – 3.30 mmol/L	> 3.30 mmol/L
CPK	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 10 × ULN	> 10 × ULN

Assessments of hepatotoxicity will be made based on a single laboratory parameter collected at any post-baseline visit through the Final Treatment visit using the following criteria:

- ALT > 5 × ULN and ≥ 2 × baseline;
- Total bilirubin ≥2 × ULN and > baseline;
- Total bilirubin ≥ 2 × ULN and > baseline and direct/total bilirubin ratio > 0.4;
- Increase from nadir by grade in ALT:
  - ALT > 3 – 5 × ULN (Grade 2);
  - > 5 – 20 × ULN (Grade 3);
  - > 20 × ULN (Grade 4).

The direct/total bilirubin ratio will be calculated using the same date/time sample corresponding to the total bilirubin elevation. For the summary of increase from nadir by grade in ALT, the post-baseline value must represent an increase from the first nadir (including baseline) to be counted, where the grade of the post-baseline value must be more extreme than the grade of the nadir value. First nadir is defined as the last value prior to the first increase. The maximum ratio relative to the ULN will be used to determine if subjects meet the criteria listed above.

Assessments of hepatotoxicity will also be made based on multiple laboratory parameters collected at any post-baseline visit through the Final Treatment visit using the following criterion:

- ALT > 3 × ULN (Grade 2 + and increase from nadir grade) and total bilirubin ≥ 2 × ULN.

For the criterion based on multiple laboratory parameters, the analysis will check to see if the subject meets the ALT and total bilirubin portions of the criterion at any time within the Treatment Period (i.e., draw dates do not need to be concurrent). The maximum ratio relative to the ULN for each parameter will be used to determine if the subject meets the criterion listed above. 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. The grade of the post-baseline ALT value must be at least Grade 2 and more extreme than the grade of the nadir value. For total bilirubin, a subject or event will be counted if the post-baseline laboratory values meet 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).

11.3.2 Statistical Methods

Clinical laboratory tests will be summarized by treatment arm (A and B) at each visit during the DB Treatment Period and separately for Arm B subjects during the OL Treatment Period. Also, summaries of clinical laboratory data collected during the Post-Treatment Period will be presented for Arm A of the safety population and separately for the OL population.

The baseline value for clinical laboratory tests will be the last non-missing measurement on or before the day of the first dose of DB 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 all summaries of the data from the DB, OL, and Post-Treatment Period visits.

Changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized. For DB Treatment Period visits and for Post-Treatment visits for Arm A, each protocol-specified laboratory parameter will be summarized with the sample size; baseline mean; visit mean; and change from baseline mean, standard

deviation, and median. The differences between the active and placebo arms in the DB Treatment Period will be analyzed using an ANOVA model with treatment arm as the factor. The difference between the treatment arms (Arm A minus Arm B) in mean change from baseline along with the corresponding 95% CI, standard error, and *P* value will be presented. For OL Treatment Period visits and Post-Treatment visits for Arm B, each protocol-specified laboratory parameter will be summarized with the sample size; baseline mean; visit mean; and change from baseline mean, standard deviation, minimum, median, and maximum.

Plots of mean change (± standard error) from baseline to each visit will be presented by treatment arm for ALT and bilirubin (total, direct, and indirect). For each parameter, mean changes at visits during the DB Treatment Period for Arms A and B along with mean changes at post-treatment visits for Arm A will be presented on the same plot, and mean changes at visits during the OL Treatment Period will be provided for Arm B on a separate plot.

Hematology and chemistry data values will be categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. Shift tables from baseline to minimum value and from baseline to maximum value during the DB and OL Treatment Periods will be created for each treatment arm. The shift tables will cross-tabulate the frequency of subjects with baseline values below/within/above the normal range versus minimum/maximum post-baseline values below/within/above the normal range.

The laboratory parameters listed in Table 15 will be categorized according to the toxicity grades defined in the table. The number and percentage of subjects with a maximum toxicity grade of 1, 2, 3 or 4 during treatment (DB treatment and OL treatment summarized separately) will be calculated for each treatment arm. 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 15, the summary will also include the number and percentage of subjects with a maximum of at least Grade 3 for each treatment arm. For summaries of data collected during the DB Treatment Period, the difference in rates between the 2 arms (Arm A minus Arm B), and

the 2-sided 95% CI for the rate difference using the Wilson score method for a difference in proportions will be presented.[12] These summaries will also be presented for the set of HCV/HIV co-infected subjects (determined at Screening) within the populations/groups specified in Section 11.1.

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 15.

For the assessments of hepatotoxicity based on single and multiple laboratory parameters, the number and percentage of subjects meeting the criterion during treatment will be calculated for each criterion. A listing of all ALT, AST, total, indirect and direct bilirubin, ratio of direct to total bilirubin, and alkaline phosphatase values will be provided for each subject who met any of the single or multiple criteria defined above. The listings will be reviewed to assess bilirubin (e.g., mixed or direct predominance) and temporal relationships for subjects with ALT > 3 × ULN (or ALT Grade 2 +) and total bilirubin ≥ 2 × ULN.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

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

The criteria for potentially clinically significant (PCS) vital sign findings are presented in Table 16.

Table 16. Criteria for Potentially Clinically Significant Vital Sign Values

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

11.4.2 Statistical Methods

Vital signs will be summarized by treatment arm at each visit during the DB Treatment Period and separately for Arm B subjects in the OL Treatment Period. Also, vital signs collected during the Post-Treatment Period will be presented for Arm A of the safety population and separately for the OL population.

The baseline value for vital signs will be the last measurement on or before the day of the first dose of DB study drug. The same baseline value will be used for all summaries of the data from the DB, OL, and Post-Treatment Period visits.

Changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized. For DB Treatment Period visits and for Post-Treatment visits for Arm A, each vital sign parameter will be summarized with the sample size; baseline mean; visit mean; and change from baseline mean, standard deviation, and median. The differences between the active and placebo arms in the DB Treatment Period will be analyzed using an ANOVA model with treatment arm as the factor. The difference between the treatment arms (Arm A minus Arm B) in mean change from baseline along with the corresponding 95% CI, standard error, and *P* value will be presented. For OL Treatment Period visits and Post-Treatment visits for Arm B, each vital sign parameter

will be summarized with the sample size; baseline mean; visit mean; and change from baseline mean, standard deviation, minimum, median, and maximum.

The number and percentage of subjects with on-treatment values (DB treatment and OL treatment summarized separately) meeting the specified criteria for PCS vital sign values (Table 16) will be calculated for each treatment arm. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A separate listing will be provided that presents all vital sign values for the subjects meeting PCS criteria during treatment.

11.5 Analysis of HIV-1 RNA and Flow Cytometry Data

Plasma HIV-1 RNA will be measured by the central laboratory using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0. For specimens with HIV-1 RNA results that are detectable but not quantifiable, the results are reported as "< 20 CP/ML HIV-1 RNA DETECTED;" for specimens with no HIV RNA detected, the results are reported as "NO HIV-1 RNA DETECTED." Subjects will also have blood samples drawn and archived. These samples may be used for other analyses including drug resistance testing. These samples may be tested at the discretion of AbbVie.

For the HCV/HIV co-infected subjects (determined at Screening) who are on HIV-1 ART at initiation of DB study drug, the numbers and percentages of subjects with 2 consecutive HIV-1 RNA values ≥ 200 copies/mL during the DB and OL Treatment Periods will be calculated for each treatment arm; only data from the central laboratory will be included in these analyses. A listing of subjects with a plasma HIV-1 RNA value ≥ 200 copies/mL at any baseline or post-baseline visit during the study will be provided. Data from the central and local laboratory will be included in the listing.

For the HCV/HIV co-infected subjects (determined at Screening), changes from baseline to each post-baseline visit, including applicable post treatment visits, in CD4+ T-cell count (absolute and percentage), CD8+ T-cell count (absolute and percentage), and lymphocytes (count) will be summarized for each treatment arm. For DB Treatment

Period visits, for Post-Treatment visits for Arm A, and for OL Treatment Period visits and Post-Treatment visits for Arm B, each protocol-specified laboratory parameter will be summarized with the sample size; baseline mean; visit mean; and change from baseline mean, standard deviation, minimum, median, and maximum.

12.0 Summary of Changes

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

1. Modified the definitions of the mITT populations to also exclude subjects who received incorrect duration of treatment due to incorrect classification of GT or treatment experience at randomization.
2. Removed the analyses of demographics, baseline characteristics, study drug exposure and compliance for the mITT populations because it is expected that these populations will be very similar to the ITT population.
3. Removed the analyses of demographics and baseline characteristics for the OL population because it is expected that this population will be very similar to the Arm B safety population.
4. Removed the analyses of study drug exposure and compliance for the GT1-infected and GT2-infected groups because these variables are expected to be similar between the set of all subjects and the GT1-infected and GT2-infected groups.
5. Replaced analyses by geographic region with analyses for the geographic region of China because analyses for the subset of subjects from China, rather than analyses by geographic region, are required by the regulatory agency. Certain analyses of subject disposition and SVR_{12} will be performed by geographic region.
6. Added additional analyses of categorical baseline characteristics for subjects with HCV/HIV co-infection at Screening to provide additional information for the HCV/HIV co-infected population.

7. Added analyses of SVR_{12} for Arm A for the geographic region of China to the sensitivity analysis to address regulatory requirements for China-specific analyses.
8. Added additional imputation approaches and assessment of homogeneity across stratification variables to the sensitivity analysis of the primary endpoints to align with the HCV ABT-493/ABT-530 program.
9. Removed the subgroup analysis of the primary endpoints for the mITT populations to align with the HCV ABT-493/ABT-530 program.
10. Added the additional efficacy analysis of the percentage of subjects with HCV virologic failure through PT Week 12 to align with the HCV ABT-493/ABT-530 program.
11. Removed several of the additional efficacy analyses to be performed on the HCV/HIV co-infected population because the number of HCV/HIV co-infected subjects is anticipated to be lower than had been expected at the time the protocol was written.
12. The PRO analysis as defined in the protocol:

    - Cumulative number and percentage of subjects who have ever experienced an increase from baseline in the FSS total score of greater than or equal to 0.7 through each applicable timepoint;

    Has been changed to below to align with the HCV ABT-493/ABT-530 program:

    - Number and percentage of subjects who have ever experienced an increase from baseline up through each applicable time point of greater than or equal to 0.7 in the FSS total score.
13. Specified the assays used by the central laboratory for the HCV RNA and HIV-1 RNA samples and the HIV-1 resistance testing, along with the LLOD and LLOQ for the HCV RNA assay. This information was not known at the time of protocol development.
14. Removed the analyses of safety data for the GT1-infected and GT2-infected groups because GT is not expected to have an impact on safety.

15. Removed several of the safety analyses to be performed on the HCV/HIV co-infected population because the number of HCV/HIV co-infected subjects is anticipated to be lower than had been expected at the time the protocol was written.
16. Added calculation of the between-arm risk difference to all AE summaries at the SOC and preferred term level during the DB Treatment Period and removed comparisons using Fisher's exact test to align with the HCV ABT-493/ABT-530 program.
17. Added calculation of the between-arm risk difference and 95% CI using Wilson's score method to AE summaries by preferred term and clinical laboratory summaries by maximum toxicity grade and removed comparisons using Fisher's exact test to align with the HCV ABT-493/ABT-530 program.
18. Added analysis of laboratory assessments of hepatotoxicity to align with the HCV ABT-493/ABT-530 program.
19. Added plots of mean change (± standard error) from baseline for ALT and bilirubin (total, direct, and indirect) to align with the HCV ABT-493/ABT-530 program.
20. Removed comparisons between arms using Fisher's exact test from PCS vital sign summaries during the DB Treatment Period to align with the HCV ABT-493/ABT-530 program.
21. Added analyses of CD4+ T-cell count, CD8+ T-cell count, and lymphocytes for the HCV/HIV co-infected population to align with the HCV ABT-493/ABT-530 program.

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Document Approval

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	15-Jan-2018 04:59:14 PM	Approver
	15-Jan-2018 05:25:19 PM	Approver
	15-Jan-2018 08:03:53 PM	Approver
	17-Jan-2018 04:31:34 PM	Approver