1.0 Title Page

Clinical Study Protocol 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

AbbVie Investigational Product:	ABT-493, ABT-530
Date:	03 April 2017
Development Phase:	3
Study Design:	This is a randomized, double-blind, placebo-controlled study.
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie)*
Sponsor/Emergency Contact:	[redacted]

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Synopsis

AbbVie Inc.	**Protocol Number:** M15-592
Name of Study Drug: ABT-493/ABT-530	**Phase of Development:** 3
Name of Active Ingredient: ABT-493/ABT-530	**Date of Protocol Synopsis:** 03 April 2017
Protocol Title: 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	
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 hepatitis C virus (HCV) GT1 to GT6 infection with or without human immunodeficiency virus (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 and 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.	
Investigators: Multicenter	
Study Sites: Approximately 50 sites	
Study Population: Chronic HCV GT1, 2, 3, 4, 5 or 6-infected Asian male and female adults aged 18 years or older, without cirrhosis, with or without HIV co-infection who are HCV treatment-naïve or treatment-experienced to interferon (IFN) (alpha, beta or pegylated interferon [pegIFN]) with or without ribavirin (RBV) OR sofosbuvir with RBV with or without IFN.	
Number of Subjects to be Enrolled: Approximately 504 subjects	
Methodology: This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety and pharmacokinetics 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 HCV treatment-experienced with IFN (alpha, beta or pegIFN) with or without RBV OR sofosbuvir with RBV with or without IFN.	

Methodology (Continued):

Approximately 504 subjects meeting the eligibility criteria will be enrolled. 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.

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 groups. In each regional Asian country, each of the GT1 and GT2-infected groups will be randomized in a 2:1 ratio to Arm A or Arm B.

Arm A:	ABT-493/ABT-530 300 mg/120 mg 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

This study will consist of three periods:

Double-Blind (DB) Treatment Period: Eligible subjects will be randomized to receive ABT-493/ABT-530 300 mg/120 mg once daily (QD) (Arm A) or placebo QD (Arm B) for 8 or 16 weeks.

Treatment duration will differ among subjects based on HCV GT and HCV treatment experience (8 weeks of treatment for GT1, 2, 3, 4, 5 and 6-infected subjects with the exception of 16 weeks for treatment-experienced GT3-infected subjects).

Scheduled visits in the DB Treatment Period for subjects assigned to receive 16 weeks of treatment will consist of Day 1 and Weeks 1, 2, 4, 8, 12, and 16; for subjects assigned to receive 8 weeks of treatment, scheduled visits will consist of Day 1 and Weeks 1, 2, 4 and 8.

AbbVie, investigators and subjects will be blinded to drug assignment, HCV virologic results and specific safety laboratory results for the duration of the DB Treatment Period. HCV virologic results will be reviewed and individual HCV virologic failure criteria will be applied to those subjects randomized to active drugs by an un-blinded independent reviewer. Upon reaching the end of the DB period or premature discontinuation of study drugs, subjects, investigators and AbbVie will be un-blinded to drug assignment for each subject. Subjects randomized to active drugs will enter the Post-Treatment (PT) Period; subjects randomized to placebo will enter the Open-label (OL) Treatment Period.

Subjects randomized to placebo who prematurely discontinue placebo during the DB Treatment Period will be eligible for open-label treatment at the final scheduled DB visit (Week 8 or Week 16) and not at the time of discontinuation of placebo.

Open-Label (OL) Treatment Period: Subjects who are randomized to the placebo arm during the DB Treatment Period (Arm B) will receive open-label ABT-493/ABT-530 300 mg/120 mg QD for either 8 or 16 weeks in the OL Treatment Period.

Treatment duration will differ among subjects based on HCV GT and HCV treatment experience (8 weeks of treatment for GT1, 2, 3, 4, 5 and 6-infected subjects with the exception of 16 weeks for treatment-experienced GT3-infected subjects).

Methodology (Continued):

In the OL Treatment Period, visits will occur at Weeks 1, 2, 4, 8, 12, and 16 for subjects assigned to receive 16 weeks of treatment; for subjects assigned to receive 8 weeks of treatment, scheduled visits will occur at Weeks 1, 2, 4 and 8. OL Day 1 will be the day after the final scheduled DB visit (Week 8 or Week 16) and subjects will not return for a visit; rather, the subjects will be instructed to take their first dose of ABT-493/ABT-530 at home. Study procedures, including assessment of adverse events, vital signs, adherence, concomitant medications, HCV RNA, HCV resistance, HIV-1 RNA and HIV resistance (as applicable), pharmacokinetic assays, and clinical laboratory tests will be conducted at each visit.

Post-Treatment (PT) Period: Subjects randomized to active drug (Arm A) who complete or prematurely discontinue study drug during the DB Treatment Period and subjects randomized to placebo (Arm B) who complete the OL Treatment Period or prematurely discontinue study drug during the OL Treatment Period, will be followed for 24 weeks to monitor safety and to evaluate efficacy and the emergence and/or persistence of HCV resistance-associated substitutions (RASs).

Baseline HCV resistance samples will be collected for all subjects, but HCV resistance analysis of baseline and post-baseline samples will be performed only for subjects who experience virologic failure.

During the PT Period, all subjects will have visits at Weeks 4, 12, and 24 following completion of either the DB Treatment Period (for subjects randomized to ABT-493/ABT-530 in the DB Treatment Period) or the OL Treatment Period (for subjects randomized to placebo in the DB Treatment Period). Study procedures to monitor safety, HCV RNA, HIV-1 RNA and HIV resistance (as applicable), and the emergence and/or persistence of HCV resistance-associated substitutions will be conducted during these visits.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female of Asian descent and at least 18 years of age at time of Screening.
2. If female, subject must be either (as defined in section 5.2.4 of the protocol) postmenopausal, OR permanently surgically sterile OR for Women of Childbearing Potential practicing at least one protocol specified method of birth control, starting at Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.
3. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.

   Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in the protocol) at Screening do not require pregnancy testing.
4. Screening laboratory result indicating HCV GT1, 2, 3, 4, 5 or 6-infection.
5. Subject has positive HCV antibody (Ab) and plasma HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.
6. Chronic HCV infection defined as one of the following:
   - Positive for HCV Ab or HCV RNA at least 6 months before Screening;
   - A liver biopsy consistent with chronic HCV infection.
7. Subject must be HCV treatment-naïve (i.e., subject has not received any approved or investigational HCV treatment) or treatment-experienced (i.e., subject has failed prior HCV treatment with IFN [alpha, beta or pegIFN] with or without RBV OR sofosbuvir with RBV with or without IFN). Previous HCV treatment must have been completed ≥ 8 weeks prior to screening.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

8. Body Mass Index (BMI) is ≥ 18.0 kg/m^2 at the time of Screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).
9. Subject must be documented as non-cirrhotic, defined as meeting one of the following criteria:
   - A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4; or
   - A FibroScan® score of < 12.5 kPa within 6 months of Screening or during the Screening Period; or
     - Subjects with indeterminate FibroScan® score (12.5 ≤ score < 14.6), must have a qualifying liver biopsy.
   - A screening FibroTest score of ≤ 0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) < 1.
     - Subjects with indeterminate FibroTest (0.48 < result < 0.75), or conflicting FibroTest and APRI results (e.g., FibroTest ≤ 0.48, but APRI ≥ 1) must have a qualifying liver FibroScan® or biopsy.
10. Must voluntarily sign and date an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of any screening or study specific procedures.
11. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

In addition to Inclusion Criteria 1 through 11, subjects enrolled with HCV GT1 to 6 and HIV-1 co-infection, must also meet the following criteria per local standard practice:

12. Positive test result for Human Immunodeficiency Virus antibody (HIV Ab) at Screening.
13. Naïve to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study)

    or

    On a stable, qualifying HIV-1 ART regimen (allowed regimens will be based on AbbVie approval) for at least 8 weeks prior to screening.
14. Subjects naïve to ART must have CD4+ count ≥ 500 cells/mm^3 (or CD4+ % ≥ 29%) at Screening.
15. Subjects on stable ART must have the following:
    - CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening; and
    - Plasma HIV-1 RNA below LLOQ by an approved plasma HIV-1 RNA quantitative assay (including but not limited to Roche COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) at Screening and at least once during the 12 months prior to Screening.

Main Exclusion:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

3. Positive test result at Screening for hepatitis B surface antigen (HBsAg) or hepatitis B virus (HBV) DNA > LLOQ if HBsAg is negative.
4. HCV genotype performed during screening indicating co-infection with more than one HCV genotype.
5. Requirement for and inability to safely discontinue contraindicated medications or supplements at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
6. Clinically significant abnormalities, other than HCV infection or HCV/HIV co-infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator, including, but not limited to:
   - Uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit.
   - Active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
   - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection.
7. Any cause of liver disease other than chronic HCV-infection, including but not limited to the following:
   - Hemochromatosis
   - Alpha-1 antitrypsin deficiency
   - Wilson's disease
   - Autoimmune hepatitis
   - Alcoholic liver disease
   - Steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection
8. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - ALT > 10 × upper limit of normal (ULN)
   - AST > 10 × ULN
   - Estimated Glomerular filtration rate adjusted for the Chinese population (eGFR) < 50 mL/min/1.73 m^2 as estimated by the MDRD method, modified for the Chinese population (C-MDRD), according to the following formula:

     $$eGFR = 175 \times (\text{Serum Creatinine})^{-1.234} \times (\text{Age})^{-0.179} \times (0.79 \text{ if Female})$$
   - Direct bilirubin > ULN
   - Albumin < lower limit of normal (LLN)
   - International normalized ratio (INR) > 1.5 × ULN, unless subject has known hemophilia or is on a stable anticoagulant regimen affecting INR
   - Hemoglobin < 11 g/dL for women; < 12 g/dL for men
   - Platelets < 90,000 cells per mm^3
   - Absolute neutrophil count (ANC) < 1000 cells/µL

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

9. History of solid organ transplantation.
10. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks (whichever is longer) prior to study drug administration.
11. Any current or past clinical evidence of decompensated liver disease such as ascites noted on physical exam, use of diuretics for ascites, hepatic encephalopathy or esophageal variceal bleeding.
12. Requirement for chronic use of systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab).
13. Chronic human immunodeficiency virus, type 2 (HIV-2) infection.
14. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-493/ABT-530.
15. History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs.
16. Patients who can't participate in study per local law.

Additional Exclusion Criteria for Subjects with HCV/HIV Co-Infection:

17. For subjects on stable ART, taking anti-retroviral agent(s) other than those permitted based on AbbVie approval.
18. Treatment for an AIDS-associated opportunistic infection (OI) within 12 months of Screening or prophylaxis for an AIDS-associated opportunistic infection within 6 months of Screening.
19. Diagnosis of any clinical AIDS-defining event within 12 months prior to Screening. A list of these events may be found in Appendix D of the protocol.

Investigational Products:	ABT-493/ABT-530 100 mg/40 mg Film-coated tablet or matching placebo
Doses	ABT-493/ABT-530 300 mg/120 mg QD (3 tablets)
Mode of Administration:	Oral

Duration of Treatment:

Subjects will receive ABT-493/ABT-530 or matching placebo for 8 or 16 weeks. Subjects assigned to receive placebo will be treated for 8 or 16 weeks with ABT-493/ABT-530 after being administered matching placebo for 8 or 16 weeks. Treatment duration will differ among subjects based on HCV GT and treatment experience (8 weeks of treatment for treatment-naïve and treatment-experienced GT1, 2, 3, 4, 5 and 6-infected subjects with the exception of 16 weeks for treatment-experienced GT3-infected subjects).

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA (IU/mL) will be assessed at each DB, OL and Post-Treatment Visit.

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-Lead ECGs, and vital signs.

Criteria for Evaluation (Continued):

Patient Reported Outcomes (PROs):

Health state utility will be measured using the EuroQol-5-Dimensions-3 Level (EQ-5D-3L) instrument. The Fatigue Severity Scale (FSS) will be used to measure the severity of fatigue and its effect on lifestyle and activities.

Resistance:

For subjects receiving active study drugs who experience virologic failure, the following HCV resistance information will be tabulated and summarized: 1) HCV amino acid variants at baseline at signature resistance-associated positions relative to the appropriate prototypic reference sequence; 2) HCV amino variants at signature resistance-associated positions relative to the appropriate prototypic reference sequence in available post-baseline samples; and 3) HCV amino acid variants relative to the baseline sequence in available post-baseline samples.

HIV-1 drug resistance genotyping for protease, reverse transcriptase and integrase sequences may be performed for protocol-defined eligible specimens.

Pharmacokinetic:

Individual plasma concentrations of ABT-493 and ABT-530, and possible metabolites of ABT-493 and ABT-530 will be tabulated and summarized. Values for pharmacokinetic parameters of ABT-493, ABT-530 and possible metabolites of ABT-493 and ABT-530 including apparent clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using population pharmacokinetic modeling procedures.

Plasma concentrations of HIV-1 ARTs for individual subjects, or a group of subjects or for the entire study may be analyzed based on safety, HCV RNA and/or plasma HIV-1 RNA results.

Statistical Methods:

The primary analysis will occur after all Arm A subjects have completed the Post-Treatment (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. 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. Data collected after this lock will be added to a new version of the database which will be cleaned and locked at the end of the study.

Efficacy:

The primary efficacy endpoint variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) for the subjects treated with ABT-493/ABT-530 in the DB Treatment Period (Arm A). In order to control the Type I error rate, a fixed sequence testing procedure will be used for the ranked primary efficacy endpoints. 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.

Statistical Methods (Continued):

Efficacy (Continued):

The three ranked primary efficacy endpoints are:

1. The percentage of Arm A subjects from the combined group of GT1 to 6-infected subjects 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% confidence interval (CI) for the percentage is > 90%.
2. The percentage of Arm A subjects from the group of GT1-infected subjects 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 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.

The secondary efficacy endpoints are:

- The percentage of Arm A subjects with on-treatment HCV virologic failure (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and
- The percentage of Arm A subjects with post-treatment relapse of HCV infection (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment, excluding re-infection), and
- The percentages of Arm A HCV/HIV co-infected subjects achieving SVR_{12}.

For the secondary endpoints, the number and percentage of Arm A subjects will be presented along with 95% Wilson score CIs. These endpoints will be summarized for the combined group of GT1 to 6-infected Arm A subjects, the group of GT1-infected Arm A subjects, and the group of GT2-infected Arm A subjects.

Additional efficacy endpoints include: SVR_4, SVR_{24}, and the percentage of subjects who relapsed after achieving SVR_{12}.

Statistical Methods (Continued):

Safety:

All subjects who receive at least one dose of study drug will be included in the safety analyses. Safety summaries will be provided for each treatment arm during the DB Treatment Period and for Arm B during the OL Treatment Period; comparisons will be made between treatment arms in the DB Treatment Period. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug) will be tabulated by primary System Organ Class (SOC) and MedDRA preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug. Change from baseline in laboratory tests and vital signs measurements to each time point of collection will be summarized, and values that meet toxicity grades (laboratory tests only) or are potentially clinically significant, according to predefined criteria, will be summarized.

PROs:

Changes from baseline in the patient reported outcome (PRO) measures at each visit will be summarized for each treatment arm; changes from baseline during the DB Treatment Period will be compared between treatment arms using ANCOVA models with a treatment group factor and the baseline score as a covariate.

Resistance:

For all subjects receiving active study drugs who experience HCV virologic failure, the HCV amino acid variants at signature resistance-associated positions in NS3 and NS5A at baseline identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving active study drugs who experience HCV virologic failure and who have an available post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the HCV amino acid variants in NS3 and NS5A identified by population or deep sequencing and comparison to the baseline sequence, 2) the HCV amino acid variants at signature resistance-associated positions in NS3 and NS5A identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence, and 3) the persistence of HCV viral amino acid variants in NS3 and NS5A by population or deep sequencing.

If any subject on stable HIV-1 ART develops a confirmed, quantifiable plasma HIV-1 RNA level (HIV-1 RNA $\geq$ 200 at one assessment and $\geq$ 500 copies/mL on repeat testing) after starting the study, the HIV-1 protease, reverse transcriptase, and integrase sequences may be analyzed.

Pharmacokinetic:

For all subjects who receive active study drug, individual plasma concentration of ABT-493, ABT-530, and possible metabolites of ABT-493 and ABT-530 will be tabulated and summarized for each visit. Additional summaries and analyses of concentration data may be performed if appropriate and useful in the interpretation of the data. Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effects modeling approach.

1.2 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APRI	Aminotransferase to platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ART	Antiretroviral therapy
AUC	Area Under the Concentration Curve
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CL/F	Apparent Oral Clearance
CPK	Creatine phosphokinase
CR/CL	Creatinine clearance
CRF	Case report form
DAA	Direct-acting antiviral agent
DB	Double-blind
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
D/C	Discontinuation
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EQ-5D-3L	EuroQol 5 Dimensions 3 Levels Health State Instrument
EU	European Union
FSS	Fatigue Severity Scale

GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
Hemoglobin A1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
IL28B	Interleukin 28B
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LCB	Lower confidence bound
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NONMEM	Non-linear mixed-effect modeling
NS3A	Nonstructural viral protein 3A
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
OATP	Organic anion transporting polypeptide
OL	Open-label
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PegIFN/RBV	Combination of pegylated-interferon alfa-2a or alfa-2b and ribavirin

PI	Protease Inhibitor
PK	Pharmacokinetic
PR	pegIFN/RBV
PRO	Patient Reported Outcome
PT	Post-Treatment
QD	Once daily
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard Deviation
SF-36v2	Short Form 36-Version 2 Health Status Survey
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class/Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR_4	Sustained virologic response 4 weeks post dosing
SVR_{12}	Sustained virologic response 12 weeks post dosing
SVR_{24}	Sustained virologic response 24 weeks post dosing
TDF	Tenofovir disoproxil fumarate
TE-PRS	Treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
V/F	Apparent Volume of distribution
WBC	White blood cells
WOCBP	Women of child-bearing potential

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the plasma concentration-time curve
AUC_{24}	AUC for the 24-hour dosing interval
β	Apparent terminal phase elimination rate constant
CL/F	Apparent oral plasma clearance
C_{max}	Maximum observed plasma concentration
C_{trough}	Pre-dose trough plasma concentration
$t_{1/2}$	Terminal phase elimination half-life
T_{max}	Time to maximum observed plasma concentration (C_{max})

Definition of Terms

Study Drug	ABT-493 and ABT-530
Study Day 1	First day of study drug (active or placebo) dosing
Treatment Period	Day 1 through last dose of study drug
DB Treatment Period	Double-Blind Treatment Period
OL Treatment Period	Open-Label Treatment Period
Post-Treatment Period	Day after the last dose of study drug through Post-Treatment Week 24 or Post-Treatment Discontinuation

2.0 Table of Contents

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3.0 Introduction

Hepatitis C viral (HCV) infection is a global health problem, with over 184 million individuals infected worldwide.[1] There are 7 identified HCV genotypes, with genotype (GT) 1 being the most prevalent worldwide. HCV GTs 2 and 3 infections are more common in Latin America (5% to 30%), Europe (20% to 40%) and Asia (30% to 45%).[2-4] HCV GT4 is commonly found in parts of Africa and the Middle East, particularly in Egypt, GT5 is primarily found in South Africa, and GT6 is primarily found in south-east Asia.[5] Depending on various risk factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis.[6] GT7 has recently been described in Central Africa.[7]

Death related to the complications of cirrhosis may occur at an incidence of approximately 4% per year; hepatocellular carcinoma occurs in this population at an estimated incidence of 1% to 5% per year.[6] Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[6] Successful treatment of HCV has been shown to significantly reduce the risk of disease progression and related mortality as well as the development of hepatocellular carcinoma.[7,8]

In Asia, sub-genotypes 1b, 2a, 2b, 3a, and GT6 are the most common causes of HCV infections.[3] The frequency of HCV infection in China varies by geographical region within the country, age, and population groups. In a report in 2007, the national prevalence in adults was estimated to be 1% to 1.9% (ranging from 0.29% to 9.6% in various geographic areas).[3] The most common HCV GTs in China are GT1 (67%) and GT2 (14%).[3]

Epidemiology of HCV in China

Chronic HCV infection is recognized as an important cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in China.[9] Epidemiological studies in the mid-1990s reported a national prevalence of 3.2%,[10] but other reports suggested a prevalence ranging from 0.29% to 9.6%.[11]

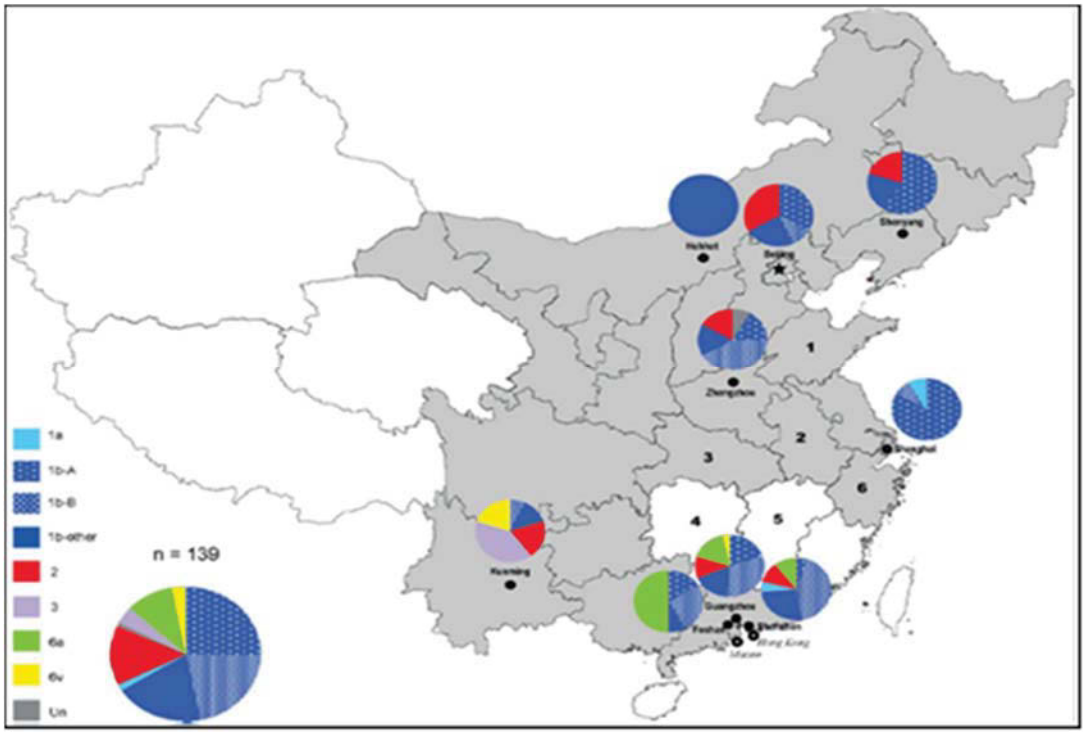
These studies showed that the frequency of HCV infection in China varied by geographical region within the country, age, and population groups and also between rural and metropolitan areas. With the Yangtze River as the boundary, the prevalence rate in northern China (3.6%) was higher than southern China (2.9%).[10] Anti-HCV positive rates were reported to increase gradually with age, from 2% in 1 year old to 3.9% in 50 to 59 year old groups, respectively.[10] A study of individuals > 55 years old in the rural Henan province found a prevalence of 9.6%,[12] while Liu et al, documented a prevalence of 0.9% in persons 25 to 65 years old in Anyang.[13]

In 2006, the National Nutritional Survey estimated that the overall national prevalence is approximately 0.43%, which represents approximately 5.1 million Chinese infected with HCV.[14] A recent study reported that 25 million Chinese were infected with HCV chronically and advanced liver diseases were frequently detected.[15] Among human immunodeficiency virus (HIV)-positive Chinese patients, it is estimated that 60% to 90% are co-infected with HCV.[14] Among patients with chronic hepatitis B, it is estimated that 11% to 15% are co-infected with HCV.[16,17] In addition, 50% of the patients receiving dialysis in China are reported to be infected with HCV.[14] Together, these data suggest that a significant number of Chinese patients are at risk for the morbidity and mortality associated with HCV infection.

An important epidemiologic feature of HCV infections in China is the distribution of GTs (Figure 1). HCV sub-genotype 1b is the most common GT in China with a prevalence of 66%,[18] but it has been reported to be as high as 90% in some areas of southern China.[14] HCV GT2 is the second most common GT, with a prevalence of 14%,[18] increasing gradually from southern to northern China (Figure 1).[14]

Other HCV GTs include GT6, which is detected in approximately 10% of cases, especially in the south region of China; and GT3 which is reported in approximately 4.3% of the cases in China.[18] Majority of these chronic HCV-infected patients in China have IL28B CC genotype.[15]

Figure 1. HCV Genotypes Distributions in China



In summary, the current epidemiology data indicate that HCV infections are an important public health problem in China and that the most prevalent GTs in the general population countrywide are HCV sub-genotype 1b and GT2. HCV GT3 and 6 are detected in the southern region of China, but their frequency is reported to be increasing in recent years.

HCV-Infection Treatment Options

Until recently, in most countries, treatment of HCV GT1 infection employed a single direct-acting antiviral agent (DAA) plus pegylated interferon and ribavirin (PR). However, interferon (IFN)-based treatment regimens are associated with considerable, often treatment limiting toxicities (fever, chills, rigor, fatigue, depression, and anemia).[19]

An oral fixed-dose combination of sofosbuvir and ledipasvir (NS5A inhibitor) was approved in the United States (US) and Europe for the treatment of GT1 and GT4 HCV

infection for non-cirrhotic and cirrhotic patients.[20] The combination achieves SVR_{12} of 94% – 96% in treatment-naïve GT1 patients with and without cirrhosis and rates of 93% in HCV GT4 infected patients with or without cirrhosis. In addition, an IFN-free combination of ombitasvir (NS5A inhibitor), paritaprevir (protease inhibitor), dasabuvir (non-nucleoside NS5b polymerase inhibitor) and ritonavir, given with or without ribavirin (RBV), was also approved in the US and Europe for the treatment of chronic HCV GT1[21] and the dual combination of ombitasvir and paritaprevir/ritonavir with RBV is approved for treatment of non-cirrhotic GT4 infection in the US[21] and for both cirrhotic and non-cirrhotic GT4 infected patients in the EU.[22] When given for 12 weeks, the dual regimen with RBV achieves 100% SVR_{12} (sustained virologic response 12 weeks post dosing) rates in the HCV GT4 infected patients without cirrhosis[23] and 96% to 100% SVR (sustained virologic response) rates in those with cirrhosis when given for 12 or 16 weeks respectively.[24]

Although IFN-free therapies are available for the treatment of GT2 and GT3 infection using sofosbuvir plus RBV,[25] SVR rates were lower for PR-treatment experienced with or without cirrhosis.[25]

Daclatasvir, an NS5A inhibitor, to be used in combination with sofosbuvir, has been approved in the US for treatment of GT3 HCV infection. However, SVR was found to be substantially reduced in patients with compensated cirrhosis.[26]

The current standard of care for the treatment of chronic HCV infection in China is pegylated interferon (pegIFN) combined with RBV for 24 weeks to 72 weeks, depending upon the patient's HCV GT, disease status, and response to past treatment(s). SVR rates range from 60% to 75% among GT1b-infected patients and 75% to 85% among primarily GT2-, GT3-, and GT6-infected patients;[27,28] however, the pegIFN/RBV regimen has a well-described burden of toxicity (e.g., severe cytopenia and depression) and cumbersome weekly injections, in addition to a long duration of treatment. Many patients requiring treatment are ineligible, and frequently toxicity is treatment limiting. Treatment of chronic HCV in China could be significantly improved with the availability of a pangenotypic, all-oral, pegIFN-free regimen that has a higher SVR rate, a better safety

profile, and shorter treatment durations. To this end, AbbVie is developing ABT-530, a next generation NS5A inhibitor, and ABT-493, a next generation protease inhibitor (PI), to be used in combination with each other for the treatment of chronic HCV.

ABT-493

ABT-493 is an NS3/4A PI with potent, and pangenotypic activity. It demonstrates a high genetic barrier to resistance and maintains activity against common variants that emerge following exposure to first generation PIs.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, and clinical data can be found in the Investigator's Brochure.[29]

ABT-530

ABT-530 is an NS5A inhibitor with potent, and pangenotypic activity. It demonstrates a high genetic barrier to resistance and maintains activity against all common single nucleotide change resistance-associated substitutions in NS5A in all GTs. ABT-530 is > 100-fold more active than the first generation NS5A inhibitors (ombitasvir, daclatasvir, and ledipasvir) against key resistance-associated substitutions. A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, and clinical data can be found in the current Investigator's Brochure.[30]

ABT-493 and ABT-530

Additive or synergistic in vitro anti-HCV activity has been demonstrated with the combination of ABT-493 and ABT-530, depending on the concentrations tested.[31]

ABT-493 and ABT-530 combination has been well tolerated when administered to over 590 healthy volunteers in Phase 1 studies (including Japanese and Han Chinese subjects living in the United States). In addition, 166 subjects were exposed to ABT-493 monotherapy and 198 subjects were exposed to ABT-530 monotherapy in Phase 2 studies. When ABT-493 was given in combination with ABT-530 in healthy volunteers, ABT-493 exposures were not significantly changed by ABT-530 (≤ 31% difference); however, the

exposure of ABT-530 increased in an ABT-493-dose-dependent manner (from 1.5-fold at 100 mg ABT-493 up to 3- to 4-fold at 400 mg ABT-493).

The combination of ABT-493 and ABT-530 has also been evaluated in overseas Han Chinese subjects at various dose combination levels (ABT-493 + ABT-530: 100 mg + 120 mg, 200 mg + 120 mg, 300 mg + 120 mg, 200 mg + 80 mg, and 700 mg + 160 mg) in Studies M14-066 and M15-432. Results from these 2 studies showed no observed ethnic differences for ABT-493 and ABT-530 at doses evaluated.

The safety profile of coadministered ABT-493 and ABT-530 in healthy volunteers in these studies is consistent with that of the individual compounds.

For a more detailed discussion of drug-drug interaction studies please refer to the Investigator's Brochures for respective compounds.[29,30]

ABT-493 + ABT-530 Combination in HCV-Infected Subjects

Data from Global Phase 2b studies demonstrated robust efficacy results for 300 mg ABT-493 in combination with 120 mg ABT-530 across HCV GTs with favorable safety profiles in HCV-infected subjects. Thus, this dose combination was proposed for the Phase 3 clinical program studies.

Phase 3 dose and treatment durations for the planned Phase 3 studies were based on available SVR_4 and SVR_{12} data from ABT-493 and ABT-530 combination Phase 2b studies (Studies M14-867 and M14-868 (Parts 1 and 2)) and exposure-response modeling and simulations of antiviral activity. Based on the results from the Phase 2b studies, Studies M14-867 and M14-868 (Parts 1 and 2), the 300 mg dose of the ABT-493 and 120 mg dose of ABT-530 in combination was proposed for global registrational studies. This dose had been demonstrated to be efficacious for the proposed Phase 3 study populations with the planned study durations and would reduce chances of virologic failures across GTs and difficult-to-treat patient populations to maximize the chance for SVR. Importantly, ABT-493 and ABT-530 regimens including the proposed 300 mg/120 mg ABT-493/ABT-530 QD regimen had been well-tolerated and safe across

all Phase 2b study arms including cirrhotic subjects. All ABT-493 and ABT-530 doses studied had a similar safety profile. The 300 mg ABT-493 and 120 mg ABT-530 dose were also supported by the exposure-response analyses and SVR simulations to achieve higher SVR rates than using lower doses of respective DAAs in the planned Phase 3 populations. Based on all current data available, AbbVie believes the combination of 300 mg ABT-493 and 120 mg ABT-530 provides optimal balance for efficacy, safety, and regimen simplicity

The 6 Global Phase 3 trials include a study in HCV GT1 – 6 in patients with Renal Impairment (Study M15-462), a study in HCV GT1 comparing 8 versus 12 weeks in subjects without cirrhosis (Study M13-590), a placebo controlled comparator trial in HCV GT2-infected subjects without cirrhosis (Study M15-464), an active comparator trial with daclatasvir plus sofosbuvir for 12 weeks in GT3 subjects without cirrhosis (Study M13-594), a dedicated GT4 – 6 non-cirrhotic trial for 12 weeks (Study M13-583) and a 12 week treatment duration Phase 3 trial evaluating subjects with HCV GT1, 2, 5 – 6 with compensated cirrhosis (Study M14-172).

Three additional Phase 3 studies were initiated in 2Q2016. The objective of these studies is to assess the efficacy and safety of the combination of ABT-493 and ABT-530 in special populations and include: HCV GT1 – 6 subjects who are status post liver transplantation (Study M13-596), HCV GT1 – 6 subjects with HIV/HCV co-infection (Study M14-730), and a study in HCV GT3 subjects without cirrhosis (expansion of Study M14-868).

Phase 2 Studies that were subsequently expanded (Studies M14-867 and M14-868) assessed efficacy, safety and pharmacokinetics of combination of ABT-493 and ABT-530 in HCV GT1 (Study M14-867 Part 1) or GT2- or 3-infected (Study M14-868 Part 1) in treatment-naïve and PR-experienced non-cirrhotic subjects, respectively, GT4 – 6 (Study M14-867 Part 2) or GT2- or 3-infected (Study M14-868 Parts 1, 2 and 3) treatment-naïve and PR-experienced subjects with and without cirrhosis.

In Study M14-867 Part 1, HCV GT1-infected subjects received either 12 weeks of ABT-493 200 mg QD + ABT-530 120 mg QD (Arm A) or ABT-493 200 mg + ABT-530 40 mg QD (Arm B). One hundred percent (40/40) of subjects treated with ABT-493 200 mg QD + ABT-530 120 mg QD for 12 weeks and 97% (38/39) of subjects treated with ABT-493 200 mg QD + ABT-530 40 mg QD for 12 weeks achieved SVR_{12}. One subject in Arm B experienced relapse at Post-Treatment Week 4.

In Study M14-867 Part 2, HCV GT1-infected subjects without cirrhosis received 8 weeks of ABT-493 300 mg QD + ABT-530 120 mg, 100% (34/34) achieved SVR_4 and 97% (33/34) achieved SVR_{12}. The one subject who did not achieve SVR_{12} died due to adenocarcinoma in the abdomen which was deemed not related to study drugs, but did have HCV RNA undetectable at last visit. In Study M14-867 Part 2, treatment-naïve and PR-experienced HCV GT1-infected subjects with compensated cirrhosis received 12 weeks of ABT-493 200 mg QD + ABT-530 120 mg, 96% (26/27) achieved SVR_{12} with one subject who relapsed at Week 4 post treatment completion.

In Study M14-867 Part 2, HCV GT4 – 6 infected treatment-naïve and PR-experienced non-cirrhotic subjects were treated with ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks. All 34 subjects (22 with HCV GT4 infection, 1 with HCV GT5 infection, and 11 with HCV GT6 infection) achieved SVR_{12}.

In Study M14-868 Part 1, HCV GT2- and GT3 subjects were randomized to receive 12 weeks of the combination regimen of ABT-493 (200 or 300 mg) and ABT-530 (40 or 120 mg) with or without twice-daily, weight based RBV (1000 or 1200 mg total daily dose).

Among 74 subjects with HCV GT2 infection in Part 1 of Study M14-868, no subject has experienced on treatment virologic failure or post-treatment relapse. Excluding one subject who was lost to follow-up, all 73 subjects with HCV GT2 infection achieved SVR_{12}. The SVR_{12} rates for each of the treatment regimens were 96% (24/25) (including a subject who was lost to follow-up) of subjects treated with ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks, 100% (24/24) of subjects treated with ABT-493

200 mg QD + ABT-530 120 mg QD for 12 weeks and 100% (25/25) of subjects treated with ABT-493 200 mg QD + ABT-530 120 mg QD + RBV for 12 weeks.

One hundred twenty-one (121) subjects with HCV GT3 infection were treated in Part 1 of Study M14-868. Among all subjects receiving the regimen tested in this study, i.e., ABT-493 300 mg and ABT-530 120 mg without RBV for 12 weeks, 93% (28/30 subjects) achieved SVR_{12}. One subject in this arm had no data available (HCV RNA < LLOQ at most recent visit) through Post-Treatment Week 12 and was counted as an SVR_{12} non-responder. One subject in this arm experienced relapse at Post-Treatment Week 4.

In Study M14-868 Part 2, among 29 treatment-naïve non-cirrhotic subjects with GT3 infection treated for 8 weeks with ABT-493 300 mg QD + ABT-530 120 mg QD, no subject experienced on-treatment virologic failure or post-treatment relapse. One of the 29 subjects had missing SVR_{12} data. Among 24 treatment-naïve cirrhotic subjects with GT3 infection treated for 12 weeks with ABT-493 300 mg QD + ABT-530 120 mg QD, no subject experienced on-treatment virologic failure or post-treatment relapse.

In Study M14-868 Part 3, GT3-infected subjects with treatment experience and/or cirrhosis were treated with ABT-493/ABT-530 300 mg/120 mg QD for 12 and/or 16 weeks. Treatment-naïve GT3-infected subjects with cirrhosis achieved a SVR_{12} rate of 98% (39/40) and treatment-experienced subjects with cirrhosis achieved a SVR_{12} rate of 96% (45/47) following 12 and 16 weeks of treatment with ABT-493/ABT-530 300 mg/120 mg QD, respectively, with no virologic failures among treatment-naïve subjects with cirrhosis. The relapse rate among treatment-experienced subjects with cirrhosis following 16 weeks of treatment was 2% (1/46). Among treatment-experienced subjects without cirrhosis, the SVR_{12} rates for the 12-week and 16-week regimens were 91% (20/22) and 96% (21/22), respectively.

To date, safety data across all Part 1 arms in Studies M14-867 and M14-868 encompassing 274 subjects treated with ABT-493 at doses 200 and 300 mg and ABT-530 at doses 40 and 120 mg (with and without RBV in Study M14-868) for 12 weeks show

that the most frequently reported adverse events were fatigue, nausea, and headache (occurring in > 5% of subjects). Most of them were Grade 1 or 2 in severity. There were no increases in the frequency or severity of any adverse event between the different regimens of ABT-493 200 mg plus 40 mg or 120 mg ABT-530, and ABT-493 300 mg plus 120 mg ABT-530.

Of the 274 subjects, there have been 4 (1.5%) treatment-emergent SAEs reported combined (all assessed as not related to ABT-493 or ABT-530): pneumonia, atrial fibrillation, B-cell lymphoma, and metastatic prostate cancer. Two subjects (0.7%; 2/274) had treatment-emergent adverse events leading to treatment discontinuation. Both were GT3-infected subjects (ABT-493/ABT-530 [200 mg/120 mg] QD + RBV) of Study M14-868. One subject with history of irritable bowel disease discontinued for Grade 2 AE of abdominal pain assessed as having a reasonable possibility of relatedness to both the DAAs and RBV. Baseline ALT elevations for this subject normalized during treatment and there were no on-treatment ALT elevations above baseline; the subject had total bilirubin elevations that were primarily indirect. The abdominal pain for this subject resolved after discontinuation from study drugs. The other subject discontinued for the aforementioned Grade 4 SAE of B-cell lymphoma for the purpose of initiating chemotherapy.

In both Studies M14-867 and M14-868, in all subjects with baseline ALT elevations, the ALT levels showed a trend toward normal or became normal with DAA treatment, and there have been no on-treatment ALT elevations above baseline. The ALT normalization pattern was similar across all arms (i.e., both ABT-493 and ABT-530 dose levels) in both studies. Other laboratory abnormalities were infrequent and were primarily associated with well-described hemolytic effect of RBV, manifesting as Grade 1 anemia in total of 4 subjects, all occurring in Study M14-868 RBV-containing arms. Observed total bilirubin elevations were Grade 1 or 2 with predominantly indirect fraction, were mostly isolated occurrences, and normalized or stabilized with continued DAA therapy. Total bilirubin elevations were primarily observed in the RBV-containing arms.

The safety of the combination regimen of ABT-493 and ABT-530 in subjects with compensated cirrhosis is investigated in Study M14-867 Part 2 (ABT-493/ABT-530 [200 mg/120 mg] QD for 12 weeks) and Study M14-868 Part 2 (ABT-493/ABT-530 [300 mg/120 mg] QD for 12 weeks with and without ribavirin or for 16 weeks without ribavirin). Based on 82 subjects with compensated cirrhosis enrolled in these arms who have received 4 weeks or more of treatment, the ABT-493 and ABT-530 regimen has demonstrated a favorable safety profile in this patient population. The majority of adverse events have been Grade 1 or 2 and there have been no treatment discontinuations.

A detailed discussion of the preclinical pharmacology and toxicology, in vitro virology and metabolism, and clinical data for ABT-493, ABT-530 and the combination of ABT-493 and ABT-530 can be found in the ABT-493 and ABT-530 Fixed-Dose Combination Investigator's Brochure.

AbbVie evaluated the combination of ABT-493 (300 mg QD) + ABT-530 (120 mg QD) in healthy Western subjects in Phase 1 drug-drug interaction (DDI) studies and in Han Chinese, Japanese and Caucasians in Study M15-432. Based on cross-study comparison, the exposures (C_{max} and AUC_{24}) in Japanese and Han Chinese subjects were comparable to the exposures observed in Western subjects. Overall, results from these studies demonstrate similar pharmacokinetic profiles between Han Chinese and Caucasian subjects and support parallel approach in the proposed China development strategy utilizing the Global Phase 3 dose.

AbbVie's IFN-free combination regimen of ABT-493 and ABT-530 provides a compelling opportunity for improving the treatment of HCV-infected patients in China and meeting significant unmet medical needs of these patients. The proposed regimen provides for an all oral, IFN-free treatment that is simpler, safer, shorter and more efficacious than currently available injection-based regimens for the treatment of HCV GT1 – 6.

Antiretroviral Therapy (ART) Drug-Drug Interaction (DDI) Studies with ABT-493 and ABT-530

Phase 1 DDI studies of the ABT-493 + ABT-530 combination with HIV antiretroviral (ARV) drugs have been conducted in healthy volunteers and/or HIV-1 infected subjects.

The ABT-493 + ABT-530 combination had no clinically meaningful impact on the exposures (≤ 80%) of evaluated ARV regimens: rilpivirine, raltegravir, dolutegravir, abacavir, lamivudine, ritonavir-boosted protease inhibitors (darunavir, lopinavir), elvitegravir, emtricitabine and tenofovir disoproxil fumarate (TDF).

Based on phase 1 DDI studies, the exposures of ABT-493 and ABT-530 were not affected by rilpivirine and raltegravir.

Dolutegravir, lamivudine and abacavir (Triumeq®) coadministered with ABT-493 + ABT-530 was evaluated in a DDI study (Study M15-584 Arm 2). Coadministration was safe and well tolerated with mild adverse events reported. The exposures of dolutegravir, lamivudine and abacavir were similar with and without coadministration with ABT-493 and ABT-530 (≤ 13% difference). ABT-493 and ABT-530 exposures were slightly lower (25% to 28%) when administered with dolutegravir, lamivudine and abacavir.

ABT-493 is a substrate of an organic anion transporting polypeptide (OATP), therefore OATP inhibitors may increase the exposures of ABT-493. When ABT-493 + ABT-530 was administered with cyclosporine (400 mg), an OATP inhibitor, ABT-493 exposure increased to 5.1-fold to that of DAAs administered alone. The observed increase in exposure, however, was not associated with clinically significant safety findings.

Protease inhibitors as a class have potential to inhibit OATP, thus the larger exposure increases in ABT-493 with ritonavir boosted protease inhibitors than with ritonavir alone may result from interaction of ABT-493 with both the protease inhibitor and ritonavir components. Cobicistat has been shown in vitro and in vivo to have similar cytochrome P-450 enzyme and transporter inhibition potential as ritonavir.

When ABT-493 was administered with ritonavir, exposure of ABT-493 was 2-fold of ABT-493 exposure alone. Coadministration of ABT-493 + ABT-530 with ritonavir boosted protease inhibitors, darunavir QD or lopinavir BID, increased ABT-493 exposures, AUC and C_{max} to 3- to 5-fold and 2.6- to 4.4-fold, respectively while exposures of ABT-530 were similar with and without darunavir QD (≤ 16% change) and increased to 1.4- to 2.5-fold with lopinavir BID. The exposures of lopinavir (≤ 24% increase) or darunavir (< 30% increase) were comparable with and without DAA coadministration. Both the regimens (darunavir QD or lopinavir BID) tested were well tolerated with mild adverse events. Therefore, coadministration of ritonavir-boosted PIs is not recommended with ABT-493/ABT-530. Coadministration of ABT-493 + ABT-530 with ritonavir boosted atazanavir was studied in a DDI study that was terminated early due to an increase in ABT-493 exposure up to 16-fold and ABT-530 exposure up to 3-fold with Grade 1 and 2 increases in ALT and Grade 2 to 3 increase in total bilirubin (predominately indirect). Therefore, coadministration of atazanavir is contraindicated with ABT-493/ABT-530.

The combination of ABT-493 +ABT-530 was evaluated with Genvoya® (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir alafenamide 10 mg QD). Coadministration was safe and well tolerated, with mild adverse events reported and one grade 3 neutropenia deemed related to the combination of Genvoya®, ABT-493 and ABT-530 in a black male subject with a low baseline ANC, leading to premature study drug discontinuation. The ABT-493 exposure increased to 3-fold and the ABT-530 exposure increased by 57%, with clinically insignificant increases in elvitegravir, cobicistat, tenofovir and emtricitabine exposures. Thus, cobicistat boosted elvitegravir will be allowed in Study M15-592.

Efavirenz induces P-gp and exposures of ABT-493 and ABT-530 in the presence of efavirenz were approximately 3- and 2-fold lower, respectively, and thus coadministration of efavirenz and efavirenz-containing regimens is not recommended with ABT-493/ABT-530.

In summary, coadministration of HIV-PIs alone, ritonavir-boosted PIs and efavirenz is not recommended with ABT-493/ABT-530. Based on the above information, cobicistat-boosted elvitegravir, dolutegravir, abacavir, lamivudine, rilpivirine and raltegravir are allowed.

For a more detailed discussion of drug-drug interaction studies please refer to the ABT-493 and ABT-530 Fixed-Dose Combination Investigator's Brochures.[32]

3.1 Differences Statement

The current study (Study M15-592) is the Phase 3 study evaluating the efficacy, safety and pharmacokinetics of the combination of ABT-493/ABT-530 in approximately 504 Asian subjects with chronic HCV GT1, 2, 3, 4, 5 or 6-infection who are HCV-treatment naïve or -experienced, without cirrhosis and with or without HIV co-infection. The current study will evaluate the selected dose and regimen of ABT-493/ABT-530 300 mg/120 mg QD using the co-formulated, fixed dose combination tablet intended for marketing for 8 or 16 (for GT3 treatment-experienced) weeks in Asian subjects. The diverse subject population to be enrolled will be representative of the intended population of subjects infected with a broad range of HCV GTs and will allow evaluation of the safety and efficacy of ABT-493/ABT-530 in Asian subjects.

3.2 Benefits and Risks

Potential benefits of treatment with ABT-493/ABT-530 include: Potent and pan-genotypic antiviral activity in vitro, higher genetic barrier to development of drug resistance across GTs compared to first generation protease and NS5A inhibitors, no need for RBV, 8 or 16 weeks of treatment, and the convenience of a once-daily regimen.

Adverse events that are known, and those not previously described, may occur with ABT-493/ABT-530 as detailed in the informed consent of this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures. Additional safety data for each DAA alone and the combination of ABT-530

and ABT-493 are detailed in Section 3.0 and in the Investigator's Brochures for the respective compounds.

Risks associated with ABT-493 and ABT-530, including the risks of toxicity, virologic failure and development of resistant mutations (Section 5.3.4), appear to be limited and manageable based upon the available data. Given the potential for SVR in this population of HCV GT1, 2, 3, 4, 5 and 6-infected subjects, the risk-benefit assessment is favorable.

4.0 Study Objective

4.1 Primary Objective

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 hepatitis C virus (HCV) GT1 to GT6 infection with or without human immunodeficiency virus (HIV) co-infection.

4.2 Secondary Objective

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.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety and pharmacokinetics 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 will consist of 3 periods as follows:

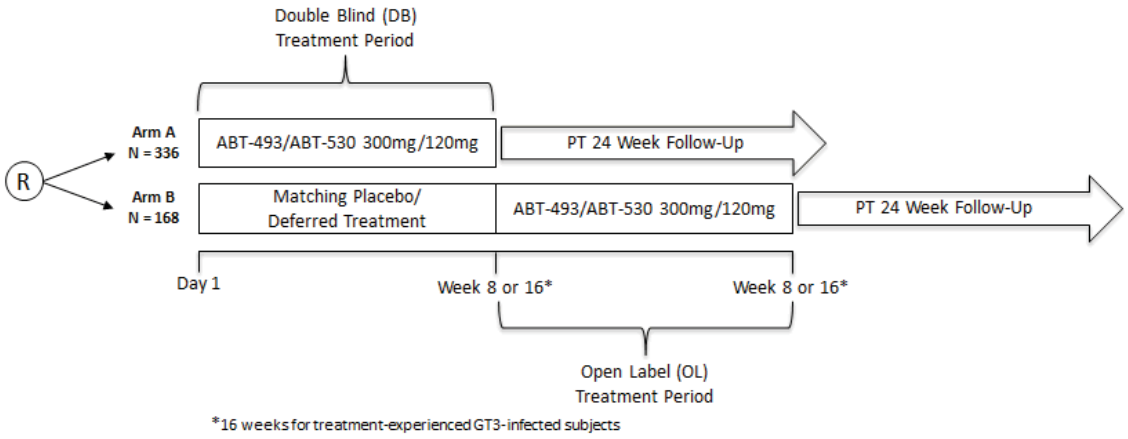
Double-Blind (DB) Treatment Period: Eligible subjects will be randomized to receive ABT-493/ABT-530 300 mg/120 mg QD (Arm A) or placebo QD (Arm B) for either 8 or 16 weeks.

Open-Label (OL) Treatment Period: Subjects who are randomized to the placebo arm during the DB Treatment Period (Arm B) will receive open-label ABT-493/ABT-530 300 mg/120 mg QD for either 8 or 16 weeks in the OL Treatment Period.

Treatment duration in both the DB and OL Treatment Periods will differ among subjects based on HCV GT and treatment-experience (8 weeks of treatment for GT1, 2, 3, 4, 5 and 6-infected subjects with the exception of 16 weeks for treatment-experienced GT3-infected subjects).

Post-Treatment Period: Subjects randomized to active drug (Arm A) who complete or prematurely discontinue study drug during the DB Treatment Period and subjects randomized to placebo (Arm B) who complete the OL Treatment Period or prematurely discontinue study drug during the OL Treatment Period will be followed for 24 weeks to monitor safety and to evaluate efficacy and the emergence and/or persistence of HCV resistance-associated substitutions.

Figure 2. 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 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

Approximately 504 subjects meeting the eligibility criteria will be enrolled. 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.

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 to Arm A or Arm B.

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, South Korea and Singapore), genotype (GT1, GT2, combined GT3 – 6), and HCV/HIV co-infection status (yes, no).

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. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in Screening will not be enrolled.

5.1.1 Screening

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study-specific procedures will receive a unique subject number via the Interactive Response Technology (IRT) system. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing, and will record the results of this assessment and the details of the informed consent process in the subject's medical records. Eligible subjects have up to 35 days following the Screening Visit to enroll into the study.

5.1.1.1 Rescreening

Subjects who at Screening have any of the following are not eligible to rescreen or retest:

- HCV GT does not meet Inclusion Criterion 4, Section 5.2.1, or meets Exclusion Criterion 4, Section 5.2.2.

Otherwise subjects may be retested or rescreened only once.

Subjects who have exclusionary laboratory parameter(s) are allowed to retest on the related panel(s) (e.g., exclusionary ALT requires a repeat chemistry panel) within the same screening period and must meet all eligibility laboratory criteria on any panel that is repeated. If the retest result(s) are also exclusionary, the subject may not be rescreened.

Subjects that are rescreened outside of the initial 35 day screening period must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary.

For subjects who rescreen or subjects that do not meet the study eligibility criteria, the site personnel must contact the IRT and identify the subject as a screen failure.

5.1.2 Double-Blind Treatment Period

After meeting the eligibility criteria, subjects will be randomized via IRT to a treatment arm. Subjects will be administered study drug at the site on Study Day 1, with dosing instructions.

Study visits and procedures during the DB Treatment Period are detailed in Appendix C. Safety and tolerability will be assessed throughout the study. Laboratory testing will include chemistry, hematology, and urinalysis as specified in Table 2. Plasma samples for pharmacokinetic analysis (including optional samples for intensive PK analysis) and HCV RNA analysis will be collected as detailed in Section 5.3.2 and Section 5.3.1.1.

AbbVie, investigators and subjects will be blinded to drug assignment and HCV virologic results for the duration of the DB Treatment Period. AbbVie, investigators and subjects will remain un-blinded to HIV virologic results for the duration of the study. HCV virologic results will be reviewed and HCV virologic failure criteria will be assessed for those subjects randomized to active drugs by an un-blinded independent reviewer. See Section 5.4.1.1 for further details. Certain safety laboratory results which could potentially be un-blinding (such as AST, ALT, and total and indirect bilirubin) will also be blinded to AbbVie, investigators and subjects. For the blinded laboratory tests, if pre-specified toxicity thresholds are exceeded then the relevant un-blinded laboratory data will be provided to the investigator and AbbVie. See Section 6.1.7 for further details. In

addition, a subject's study drug assignment may be un-blinded as directed by the toxicity management guidelines or at the investigator's discretion, if deemed necessary for subject safety.

All subjects will continue to return to the site on an outpatient basis as outlined in Appendix C. Sites should ensure that subjects adhere to all study visits. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

At the final scheduled DB Period visit (Week 8 or Week 16), the study drug will be un-blinded and subjects randomized to placebo (Arm B) who complete the DB Treatment Period may enter the OL Treatment Period and receive 8 or 16 weeks of open-label ABT-493/ABT-530.

Subjects who prematurely discontinue from the DB Treatment Period should return for a Treatment Discontinuation (D/C) Visit and undergo the study procedures as outlined in Appendix C and as described in Section 5.4.1. Ideally, this should occur on the day of study drug discontinuation, but is recommended to be no later than 2 days after their final dose of study drug in the DB Period and prior to the initiation of any other anti-HCV therapy. At the Treatment D/C Visit, subjects will be un-blinded to study drug assignment.

Subjects who were randomized to active study drug (Arm A) will immediately start the PT Period and be monitored for virologic failure and resistance as detailed in Section 5.1.4. Subjects who prematurely discontinue study drugs during the DB Treatment Period and who are found to be on placebo may elect to remain in the study (at the investigator's discretion) and receive active drug during the OL Treatment Period. However, the subject is expected to continue to attend all remaining DB Treatment Period study visits and perform all remaining study procedures through the final scheduled DB Treatment Period visit (Week 8 or Week 16) in order to be enrolled into the OL Treatment Period.

Subjects who complete or prematurely discontinue from treatment will be monitored for safety, HCV RNA, and the emergence and/or persistence of HCV resistance-associated substitutions, plasma HIV-1 RNA, HIV resistance (as applicable) and PROs in the 24-week PT Period as detailed in Section 5.1.4.

5.1.3 Open-Label Treatment Period

After completing the DB Treatment Period, subjects initially randomized to placebo (Arm B) at the beginning of the DB Treatment Period will receive 8 or 16 weeks of open-label ABT-493/ABT-530. Subjects will be provided dosing instructions and will be dispensed study drug at the final scheduled DB Treatment Period visit (Week 8 or Week 16). Administration of ABT-493/ABT-530 will start the next day (OL Day 1). The same type of bottles as used for placebo will be used for active study drug ABT-493/ABT-530.

Sites must call subjects within 4 days after the final scheduled DB Treatment Period visit (Week 8 or Week 16) to verify the first day of open-label, study drug administration and record this date on the eCRF and in the source documents. Study drugs, virologic results and safety laboratory results will not be blinded during the OL Treatment Period. Virologic failure criteria and toxicity management will be evaluated and applied by the investigator (Section 5.4.1.1 and Section 6.1.7).

Subjects who prematurely discontinue from the OL Treatment Period should return for a Treatment D/C Visit and undergo the study procedures as defined in Appendix C and as described in Section 5.4.1. Ideally, this should occur on the day of study drug discontinuation, but is recommended to be no later than 2 days after their final dose of study drugs and prior to the initiation of any other anti-HCV therapy. Subjects who complete or discontinue the OL Treatment Period will be monitored for safety, HCV RNA, the emergence and persistence of resistant viral variants, plasma HIV-1 RNA and HIV resistance (as applicable) in the 24-week Post-Treatment Period as detailed in Section 5.1.4.

5.1.4 Post-Treatment Period

All subjects who received at least one dose of active study drug and either complete treatment or prematurely discontinue the active study drug in either the DB or OL Treatment Periods will be monitored in the Post-Treatment Period for safety, HCV RNA and the emergence and persistence of resistant viral variants, plasma HIV-1 RNA and HIV resistance (as applicable) for an additional 24 weeks following the last dose of active study drug. Subjects in Arm A who receive at least one dose of active study drug in the DB Treatment Period will also be monitored in the Post-Treatment Period for PROs for 24 weeks following the last dose of active study drug.

The Post-Treatment Period will begin the day following the last dose of active study drugs (in either the DB Treatment Period for subjects who were randomized to Arm A or the OL Treatment Period for subjects who were randomized to Arm B).

Some of the Post-Treatment Period study visits and visit activities (including but not limited to vital signs, clinical laboratory tests and concomitant medication assessment) may be conducted in the home or non-hospital/clinic environment at the request of the investigator and with the agreement of the subject.

Subjects who prematurely discontinue the Post-Treatment Period should return to the site for a Post-Treatment D/C Visit as outlined in Appendix C.

5.2 Selection of Study Population

The study population consists of chronic HCV GT1, 2, 3, 4, 5 or 6-infected Asian, male and female adults, without cirrhosis, with or without HIV co-infection who are HCV treatment-naïve or treatment-experienced to IFN (alpha, beta or pegIFN) with or without RBV OR sofosbuvir with RBV with or without IFN.

5.2.1 Inclusion Criteria

1. Male or female of Asian descent and at least 18 years of age at time of Screening.

2. If female, subject must be either (as defined in section 5.2.4) postmenopausal, OR permanently surgically sterile OR for Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control starting at Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

   No male contraception is required if the male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

3. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.

   Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in the protocol) at Screening do not require pregnancy testing.

4. Screening laboratory result indicating HCV GT1, 2, 3, 4, 5 or 6-infection.

5. Subject has positive HCV antibody (Ab) and plasma HCV RNA viral load ≥ 1000 IU/mL at Screening Visit.

6. Chronic HCV infection defined as one of the following:

   - Positive for HCV Ab or HCV RNA at least 6 months before Screening;
   - A liver biopsy consistent with chronic HCV infection.

7. Subject must be HCV treatment-naïve (i.e., subject has not received any approved or investigational HCV treatment) or treatment-experienced (i.e., subject has failed prior HCV treatment with IFN [alpha, beta or pegIFN] with or without RBV OR sofosbuvir with RBV with or without IFN). Previous HCV treatment must have been completed ≥ 8 weeks prior to screening.

8. Body Mass Index (BMI) is ≥ 18.0 kg/m^2 at the time of Screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).

9. Subject must be documented as non-cirrhotic, defined as meeting one of the following criteria:
    - A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4; or
    - A FibroScan® score of < 12.5 kPa within 6 months of Screening or during the Screening Period; or
        - Subjects with indeterminate FibroScan® score (12.5 ≤ score < 14.6), must have a qualifying liver biopsy.
    - A screening FibroTest score of ≤ 0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) < 1.
        - Subjects with indeterminate FibroTest (0.48 < result < 0.75), or conflicting FibroTest and APRI results (e.g., FibroTest ≤ 0.48, but APRI ≥ 1) must have a qualifying liver FibroScan® or biopsy.
10. Must voluntarily sign and date an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of any screening or study specific procedures.
11. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

In addition to Inclusion Criteria 1 through 11, subjects enrolled with HCV GT1 to 6 and HIV-1 co-infection, must also meet the following criteria per local standard practice:

12. Positive test result for Human Immunodeficiency Virus antibody (HIV Ab) at Screening.
13. Naïve to treatment with any ART (and have no plans to initiate ART treatment while participating in this study)

    or

On a stable, qualifying HIV-1 ART regimen (allowed regimens will be based on AbbVie approval) for at least 8 weeks prior to screening.

14. Subjects naïve to ART must have CD4+ count ≥ 500 cells/mm^3 (or CD4+ % ≥ 29%) at Screening.

15. Subjects on stable ART must have the following:
    - CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening; and
    - Plasma HIV-1 RNA below LLOQ by an approved plasma HIV-1 RNA quantitative assay (including but not limited to Roche COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) at Screening and at least once during the 12 months prior to Screening.

Rationale for Inclusion Criteria

1, 4 – 7, 9, 12 – 15	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
2, 3	The impact of ABT-493 and ABT-530 on pregnancies is unknown
8	For the safety of study subjects
10, 11	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator.

3. Positive test result at Screening for hepatitis B surface antigen (HBsAg) or hepatitis B virus (HBV) DNA > LLOQ if HBsAg is negative.
4. HCV genotype performed during screening indicating co-infection with more than one HCV genotype.
5. Requirement for and inability to safely discontinue contraindicated medications or supplements listed in Table 1 at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
6. Clinically significant abnormalities, other than HCV infection or HCV/HIV co-infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator, including, but not limited to:
    - Uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit.
    - Active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
    - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection.
7. Any cause of liver disease other than chronic HCV-infection, including but not limited to the following:
    - Hemochromatosis
    - Alpha-1 antitrypsin deficiency
    - Wilson's disease
    - Autoimmune hepatitis
    - Alcoholic liver disease
    - Steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection

8. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - ALT > 10 × upper limit of normal (ULN)
   - AST > 10 × ULN
   - Estimated Glomerular filtration rate adjusted for the Chinese population (eGFR) < 50 mL/min/1.73 m^2 as estimated by the MDRD method, modified for the Chinese population (C-MDRD), according to the following formula:

     $$eGFR = 175 \times (\text{Serum Creatinine})^{-1.234} \times (\text{Age})^{-0.179} \times (0.79 \text{ if Female})$$
   - Direct bilirubin > ULN
   - Albumin < lower limit of normal (LLN)
   - International normalized ratio (INR) > 1.5 × ULN, unless subject has known hemophilia or is on a stable anticoagulant regimen affecting INR
   - Hemoglobin < 11 g/dL for women; < 12 g/dL for men
   - Platelets < 90,000 cells per mm^3
   - Absolute neutrophil count (ANC) < 1000 cells/µL
9. History of solid organ transplantation.
10. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks (whichever is longer) prior to study drug administration.
11. Any current or past clinical evidence of decompensated liver disease such as ascites noted on physical exam, use of diuretics for ascites, hepatic encephalopathy or esophageal variceal bleeding.
12. Requirement for chronic use of systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab).
13. Chronic human immunodeficiency virus, type 2 (HIV-2) infection.
14. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-493/ABT-530.

15. History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs.
16. Patients who can't participate in study per local law.

Additional Exclusion Criteria for Subjects with HCV/HIV-1 Co-Infection:

17. For subjects on stable ART, taking anti-retroviral agent(s) other than those permitted based on AbbVie approval.
18. Treatment for an AIDS-associated opportunistic infection (OI) (see Appendix D) within 12 months of screening or prophylaxis for an AIDS-associated opportunistic infection within 6 months of screening.
19. Diagnosis of any clinical AIDS-defining event within 12 months prior to screening. A list of these events may be found in Appendix D.

Rationale for Exclusion Criteria

1, 6, 8, 9, 11, 14 – 19	In order to ensure safety of the subjects throughout the study
2, 5, 10,12, 13	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
3, 4, 7	To exclude subjects with hepatitis B and liver diseases other than HCV

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or traditional Chinese medicine and/or herbal supplements) that the subject is receiving from the time of signing the consent through the DB and OL Treatment Periods and 30 days after study drugs are stopped, must be recorded in the electronic case report form (eCRF) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. The investigator should review all concomitant medications for any potential interactions.

Information regarding each subject's qualifying, stable HIV-1 ART medications (allowed regimens will be based on AbbVie approval) including start date, dose and frequency will be recorded into the eCRF at screening. In addition, subjects will be requested to record information for the last two doses of their HIV-1 ART medications taken (dosing date, times, and number of pills) prior to the study visits detailed in Appendix C, and site personnel will record this information in the eCRF.

During the Post-Treatment Period, all medications taken will be recorded until 30 days following the last dose of study drugs. Only medications taken for SAEs and for treatment of HCV and HIV will be recorded thereafter.

The AbbVie Primary Therapeutic Area Medical Director (TA MD) should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior HCV Therapy

Subjects will be considered treatment-experienced if they have failed prior HCV treatment with IFN [alpha, beta or pegIFN] with or without RBV OR sofosbuvir with RBV with or without IFN. Previous HCV-treatment must have been completed ≥ 8 weeks prior to the Screening Visit.

Subjects will be categorized as follows:

- **Treatment-naïve:** subject never received any treatment for HCV infection.
- Subjects with **an allowed prior treatment** will be categorized as follows:
- **Non-responder:** HCV RNA detected at the end of a prior treatment course (except for breakthrough, which is captured separately). These subjects are further categorized as:
    - *Null responder:* failed to achieve a 1 $\log_{10}$ IU/mL reduction in HCV RNA by Week 4 or a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course;

- *Partial responder:* achieved at least a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior treatment course but failed to achieve HCV RNA undetectable at the end of treatment;
- *Unknown or Unable to Specify:* insufficient data to categorize as null or partial responder.

- **Breakthrough:** confirmed $\geq$ 1 $\log_{10}$ IU/mL increase from nadir or achieved HCV RNA undetectable (or unquantifiable) during a prior treatment course but HCV RNA was quantifiable during or at the end of treatment.
- **Relapse:** achieved HCV RNA undetectable at the end of a prior treatment course but HCV RNA was detectable following cessation of therapy.
- **Other:** subject received a prior treatment course and reason for not achieving SVR is other than above.
- **Unknown:** subject received a prior treatment course and reason for not achieving SVR is unknown.

Subjects must have discontinued prior HCV therapy at least 8 weeks prior to the Screening Visit in order to be eligible for the study.

5.2.3.2 Prior and Concomitant HIV-1 Therapy

Subjects with HCV/HIV co-infection who are not naïve to HIV ARTs must be on a stable, qualifying HIV-1 ART regimen (allowed regimens will be based on AbbVie approval) for at least 8 weeks prior to screening.

Information regarding each subject's qualifying, stable HIV-1 ART medications including start date, dose and frequency will be recorded into the eCRF at screening. In addition, subjects will be requested to record information for the last two doses of their HIV-1 ART medications taken (dosing date, times, and number of pills) prior to the study visits during the DB and OL Treatment Periods and the Post-Treatment Period detailed in Appendix C, and site personnel will record this information in the eCRF.

Study participants should plan to remain on the same HIV-1 ART regimen for the entire study (both the DB and OL Treatment Periods and Post-Treatment Period). Any change

in the HIV-1 ART regimen during the DB or OL Treatment Period must be discussed with the AbbVie TA MD prior to the change being made, unless the change is being made to address an immediate safety concern.

5.2.3.3 Concomitant Therapy

Subjects should be on stable doses of concomitant medications for at least 2 weeks prior to the initiation of study drugs (8 weeks prior to screening for HIV ARTs). The investigator should confirm that a concomitant medication/supplement can be safely administered with study drugs. Some concomitant medications may require dose adjustments due to the potential for drug-drug interactions. The investigator can also review the label(s) for the concomitant medication(s) for additional information.

The use of hepatoprotective medication (e.g., Sho-saiko-to, Milk thistle, ursodeoxycholic acid, glycyrrhizin acid, SAMe, etc.) is allowed, provided that the drug does not meet any other exclusion criterion.

A subject on a stable dose of a hepatoprotectant should have been on the same dose for at least 2 weeks prior to study entry which begins when the subject signs the informed consent. In addition, the subject should maintain the hepatoprotectant at the same dose throughout the whole study until the end of the Post-Treatment Period. If any change to hepatoprotectant dosing is needed, the investigator should contact the AbbVie TA MD to discuss prior to taking action.

During the Post-Treatment Period, investigators should reassess concomitant medications/supplements, and subjects may resume previously prohibited medications/supplements or revert to pre-study doses after 30 days following discontinuation of active study drugs, as applicable.

5.2.3.4 Prohibited Therapy

Subjects must be able to safely discontinue any prohibited medications or supplements listed in Table 1 at least 2 weeks or 10 half-lives (whichever is longer) prior to the

first dose of any study drug and not use these during the entire DB or OL Treatment Periods and for 30 days following discontinuation of active study drugs.

Table 1. Prohibited Medications and Supplements

Medication or Supplement Name
Red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine Efavirenz containing regimens

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drugs. Subjects receiving these statins should either switch to pravastatin or rosuvastatin prior to the first dose of study drugs or may interrupt statin therapy throughout the treatment period and until 30 days after the last dose of study drug, based on the investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drugs.

Use of ethinyl estradiol containing oral contraceptives with ABT-493 and ABT-530 combination was associated with ALT increases in some healthy female subjects. Hormonal contraceptives (including oral, topical [including vaginal rings], injectable, or implantable varieties) containing ethinyl estradiol may not be used from 2 weeks prior to the first dose of ABT-493/ABT-530 until 30 days after the end of ABT-493/ABT-530 dosing. Progestin-only contraceptives, such as those containing norethindrone, desogestrel, or levonorgestrel, without ethinyl estradiol, may be used with ABT-493/ABT-530. Post-menopausal hormone replacement therapy, such as with esterified or conjugated estrogens, i.e., not containing ethinyl estradiol, may be used with ABT-493/ABT-530 at the discretion of the Investigator.

Anti-HCV medications other than those specified in the protocol will not be allowed anytime during any of the Treatment Periods.

The chronic use of systemic immuno-suppressants is prohibited from 2 weeks prior to the first dose of study drug and until 30 days after the last dose of study drug including, but

not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab).

For HCV/HIV-1 Co-Infected Subjects

The investigator must refer to the current package insert(s) or product label(s) of the subject's ART regimen for a complete list of prohibited medications.

5.2.4 Contraception Recommendations

If female, subject must be either –

- Postmenopausal defined as:
  - Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause.
  - Age < 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

    OR
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

  OR
- Women of Childbearing Potential (WOCBP):
  - Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug–
    - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
    - Bilateral tubal occlusion/ligation.
    - Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
    - Intrauterine device (IUD).

- Intrauterine hormone-releasing system (IUS), excluding ethinyl estadiol.
- Male or female condom with or without spermicide.
- Cap, diaphragm or sponge with spermicide.
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

If the male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

If the male subject is sexually active with female partner(s) of childbearing potential, he must agree from Study Day 1 through 90 days after the last dose of study drug to practice contraception with:

- Condom use and female partner(s) using at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
- Additionally, male subject agrees not to donate sperm from Study Day 1 through 90 days after the last dose of study drug.

5.3 Efficacy, Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures are described in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

Informed Consent Information

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical History

A complete medical history, including history of alcohol, tobacco and nicotine-containing product use, will be taken at Screening. The medical history will be updated on Study Day 1. The medical history obtained prior to the first dose of study drug will serve as the baseline for clinical assessment.

Physical Examination

Physical examinations will be performed at visits specified in Appendix C, or upon subject discontinuation. A symptom-directed physical examination will be performed when necessary. The physical examination performed on DB Treatment Period Day 1 will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after dosing will be recorded as adverse events.

Height will be measured only at Screening. Waist circumference will be measured at the Screening Visit, but if it is not measured at Screening, it may be measured on Day 1.

Vital Signs and Weight

Body temperature, blood pressure, pulse and weight will be measured at each study visit as specified in Appendix C or upon subject discontinuation. The subject will wear lightweight clothing and no shoes during weighing. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The vital signs measurements on Day 1 will serve as the baseline measurements for clinical assessment.

12-Lead Electrocardiogram (ECG)

A single 12-lead resting ECG will be obtained at the visits indicated in Appendix C or upon subject discontinuation. The ECG obtained at Screening will serve as the baseline assessment in the DB and OL Treatment Periods. The ECG should be performed prior to blood collection.

Each ECG will be evaluated by an appropriately qualified physician at the site ("local reader"), preferably a cardiologist. This reading of the ECG will be used by the investigator for subject safety assessments, including adverse event determination and management, and decision on whether a subject will be discontinued from the study.

The local reader will sign and date all the ECGs collected in this study and provide a global interpretation for each ECG using the following categories:

- Normal ECG
- Abnormal ECG – Not clinically significant (NCS)
- Abnormal ECG – Clinically significant (CS)

All local reader's evaluations of ECGs will be entered into the electronic source documents, electronic case report forms or paper case report forms. All ECG source documentation will be retained at the study site. The automatic cardiograph reading (i.e., cardiograph-generated measurements and interpretations) will not be collected for analysis.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests listed in Table 2 at the visits indicated in Appendix C.

The blood samples for serum chemistry tests should be collected following a minimum 8-hour fast prior to study drug intake (with the exception of the Screening Visit, which may be non-fasting). Subjects whose visits occur prior to the morning dose of study drug should be instructed to fast after midnight until the blood sample is collected in the morning and thereafter take their study medications with food. Subjects whose visits occur following the morning dose of study drug should be instructed to fast after breakfast until the study visit occurs. At the Double-Blind Study Day 1 visit, a fasting blood sample should be collected prior to the first dose of study drug. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting or non-fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A central laboratory will be utilized to process and provide results for the clinical laboratory tests.

During the DB Treatment Period, measures to prevent implicit un-blinding by laboratory results will be used. Specifically, the results of HCV RNA, ALT, AST, and bilirubin (indirect and total), will be blinded to the investigator, subject and AbbVie until the final scheduled DB Period visit (Week 8 or Week 16) or Premature D/C Visit, unless criteria for virologic failure or relevant predefined toxicity are met, in which case the relevant laboratory data will be un-blinded to the investigator, subject and AbbVie, see Section 5.4.1.1, Section 5.5.5 and Section 6.1.7.

Instructions regarding the collection, processing, and shipping of these samples can be found in the laboratory manual provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is Covance.

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Other Tests
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands, if detected Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) Reticulocyte count Prothrombin Time/INR Activated partial thromboplastin time (aPTT)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Direct and indirect bilirubin Alanine aminotransferase (SGPT/ALT) Aspartate aminotransferase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric Acid Cholesterol Total protein Glucose Triglycerides Low Density Lipoproteins (LDL)[a,b] High Density Lipoprotein (HDL)[b] Albumin Chloride Bicarbonate Magnesium Total insulin Gamma-glutamyl transferase (GGT) Creatinine clearance (Cockcroft Gault calculation) Creatine phosphokinase (CPK)[c] Follicle stimulating hormone (FSH)[d] eGFR (C-MDRD)[e]	HBsAg[f] HBV DNA (if HBsAg is negative)[f] HCV Ab[f] HIV Ab[f] Opiates[f] Barbiturates[f] Amphetamines[f] Cocaine[f] Benzodiazepines[f] Alcohol[f] Phencyclidine[f] Propoxyphene[f] Methadone[f] Hemoglobin A1C[f] HCV genotype and sub-type[f] Urine and Serum: Human Chorionic Gonadotropin (hCG) for females[g] Hepatitis B Panel[h] HCV RNA Plasma HIV-1 RNA[i] HIV-1 genotypic resistance testing (as applicable)i CD4,[i] CD4%[i] CD8,[i] CD8%[i] CD4:CD8[i] IL28B Alpha2-macroglobulin[j] Haptoglobin[j] Apolipoprotein A1[j]
Urinalysis		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Microscopic (reflex)		

a. Directly Measured.

b. Performed only at Baseline.

c. Performed during the Double-Blind Treatment Period.

d. FSH at Screening only for female subjects to assess postmenopausal state.

e. eGFR calculated by the MDRD formula, modified for the Chinese population (C-MDRD).

f. Performed only at Screening.

g. Pregnancy testing is not required for females of non-childbearing potential.

Table 2. Clinical Laboratory Tests (Continued)

h. Performed for management of transaminase elevations (Section 6.1.7.1).
i. Only for HCV/HIV co-infected subjects.
j. Component of FibroTest collected only if needed during the Screening Period.

For any laboratory test value outside the reference range that the investigator considers clinically significant:

- The investigator will repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study or study drug or requires a subject to receive treatment will be recorded as an adverse event.

The management of laboratory abnormalities that may occur during the study is described in Section 6.1.7.

Pregnancy Test

A serum pregnancy test will be performed for all female subjects of childbearing potential at Screening. Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result. Additional urine pregnancy tests will be performed at all the visits indicated in Appendix C. Pregnancy testing is not required for females of non-childbearing potential. Determination of postmenopausal status will be made during the Screening period, based on the subject's history.

Concomitant Medication Assessment

Use of medications (prescription or over-the-counter, including vitamins, herbal supplements, and vaccines) from the time of signing the consent, through the DB (and OL, if applicable) Treatment Period, and 30 days after active study drugs are stopped must be recorded in the eCRF at each study visit indicated in Appendix C. Thereafter,

only medications taken for SAEs and treatment of HCV and HIV will be recorded in the eCRF at each study visit indicated in Appendix C (Post-Treatment Period).

Hepatitis and HIV Screen

HBsAg (hepatitis B surface antigen), HBV DNA (if HBsAg is negative), HCV Ab and HIV Ab tests will be performed at Screening. The tests will be performed by a certified laboratory. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results per local regulations, if necessary.

Urine Screens for Drugs of Abuse

A urine screen for drugs of abuse will be performed at Screening. The panel for drugs of abuse will minimally include drugs listed in Table 2. Any positive result must be assessed for clinical significance.

These analyses will be performed by the certified central laboratory chosen for the study.

Liver Diagnostic Testing

Subjects who have not had a qualifying liver biopsy within the previous 24 months or who have not had a qualifying FibroScan® within the previous 6 months but otherwise meet all of the inclusion criteria and none of the exclusion criteria will undergo liver biopsy or non-invasive testing (FibroTest and APRI or FibroScan®) for assessment of cirrhosis prior to enrollment. Selection of liver biopsy or non-invasive testing performed should be based on local standard practice.

Biopsy results as per METAVIR, Batts Ludwig, Knodell, IASL, Scheuer, or Laennec gradings with fibrosis score of ≤ 3, or Ishak grading with fibrosis score of ≤ 4 are acceptable for ascertaining absence of cirrhosis. Subjects with historical liver FibroScan® or biopsy results are acceptable if these were conducted within 6 or 24 months from Screening, respectively and the results are not exclusionary. In a subject with an indeterminate FibroTest result (0.48 < result < 0.75), or conflicting FibroTest and APRI

results (e.g., FibroTest ≤ 0.48, but APRI ≥ 1) at Screening, liver FibroScan® or biopsy can be performed during Screening to ascertain the presence or absence of cirrhosis. Subjects with indeterminate FibroScan® score (12.5 ≤ score < 14.6) may only be enrolled if they have a qualifying liver biopsy performed within 24 months prior to or during Screening.

Patient Reported Outcomes (PRO) Instruments (Questionnaires)

Subjects will complete the self-administered PRO instruments (where allowed per local regulatory guidelines) on the study days specified in Appendix C. Subjects should be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaires to them. Site personnel should encourage completion of each instrument at all specified visits and should ensure that a response is entered for all items.

EuroQol-5 Dimensions-3 Level (EQ-5D-3L)

The EQ-5D-3L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-3L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 3 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subjects also rate their perception of their overall health on a separate visual analogue scale (VAS). The EQ-5D-3L should require approximately 5 minutes to complete.

Fatigue Severity Scale (FSS)

The FSS measures the impact of fatigue over the past week on specific types of functioning (e.g., motivation, exercise, physical functioning, carrying out duties, interfering with work, family, or social life). 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. The scale's psychometric properties have been confirmed in chronic

hepatitis C and other diseases. The FSS should require approximately 5 minutes to complete.

PRO instruments should be completed prior to drug administration on Study Day 1 and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

Enrollment and Assignment of Subject Numbers

All screening activities must be completed and reviewed prior to enrollment. Subjects who meet all the Inclusion Criteria and none of the Exclusion Criteria at Screening will proceed to randomization via the IRT system on DB Study Day 1.

Screening numbers will be unique 6-digit numbers and will begin with 100101 with the first three digits representing the investigative site, and the last three digits representing the subjects at that site. Randomized subjects will keep their screening number as their subject number throughout the study. Subjects will be enrolled at the DB Day 1 visit as described in Section 5.5.3 and will receive a separate unique 5-digit randomization number that will be recorded automatically in the eCRF through the IRT system. The randomization number will be used only by AbbVie for loading the treatment schedule into the database.

Study Drug Compliance for Kits

Individual kits of ABT-493/ABT-530 or matching placebo will be provided for subject dosing to the site. Each subject will have compliance documented by the site in the subject's source notes for ABT-493/ABT-530 or placebo. At each Study Drug Accountability Visit, the overall number of tablets of ABT-493/ABT-530 or placebo remaining in each bottle will be recorded in the source and entered in the IRT system along with the date of reconciliation.

HCV Genotype and Sub-Genotype

Plasma samples for HCV genotype and sub-genotype determination will be collected at Screening. Genotype and sub-genotype will be assessed using the appropriate assay by the central laboratory.

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Appendix C. Plasma HCV RNA levels will be determined by an approved HCV RNA quantitative assay for each sample collected by the central laboratory (including but not limited to Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0).

HCV Resistance Testing Sample

A plasma sample for HCV resistance testing will be collected prior to dosing on Day 1 in the DB Treatment Period and at the study visits indicated in Appendix C. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory, AbbVie, or its designee.

Flow Cytometry, HIV-1 RNA and HIV Resistance Testing Samples

Samples for plasma HIV-1 RNA levels and flow cytometry (including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]) will be obtained at the times specified in Appendix C.

If a subject who is on stable HIV-1 ART has an HIV-1 RNA level ≥ 200 copies/mL, the subject's HIV-1 RNA is to be repeated as noted in Section 5.4.1.2. At the time the repeat plasma HIV-1 RNA is drawn, a sample may be obtained for HIV-1 genotypic resistance testing. If the subject's repeat HIV-1 RNA is ≥ 500 copies/mL, the sample obtained for HIV-1 genotypic resistance testing may be analyzed as indicated by local standard of care.

If the subject's repeat HIV-1 RNA is < 200 copies/mL, then the subject will resume routine plasma HIV-1 RNA assessments as shown in Appendix C and described in Section 5.4.1.2.

Specific instructions for preparation and storage of flow cytometry, plasma HIV-1 RNA, and HIV resistance samples, if applicable, will be provided by the central laboratory, AbbVie, or its designee.

Archive Plasma Sample

Archive plasma samples will be collected at the study visits, indicated in Appendix C. Archive plasma samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by AbbVie.

Specific instructions for preparation and storage of archive samples will be provided by the central laboratory, AbbVie, or its designee.

5.3.1.2 Meals and Dietary Requirements

Study drugs, both ABT-493/ABT-530 and matching placebo should be taken with food.

5.3.1.3 Blood Samples for Pharmacogenetic Analysis

Specific instructions for collection, storage and shipment of pharmacogenetic samples will be provided by the central laboratory, AbbVie, or its designee.

IL28B Sample

One (required) whole blood sample for DNA isolation will be collected from each subject at Study Day 1 in the DB Treatment Period for Interleukin 28B (IL28B) pharmacogenetic analysis. If the IL28B pharmacogenetic sample is not collected on DB Study Day 1, it may be collected at any other visit during the study. This sample will not be used for any testing other than IL28B GTs.

Optional Sample for Pharmacogenetic Analysis

A separate (optional) whole blood sample for DNA isolation will be collected at baseline on Study Day 1 from each subject who consents. If the optional pharmacogenetic sample is not collected on Study Day 1, it may be collected at any other visit during the study. The procedure for obtaining and documenting informed consent is discussed in Section 9.3. Samples collected in China will be shipped frozen to the central laboratory in China and then to an AbbVie designated laboratory in China for long-term storage. Samples collected outside of China will be sent to an AbbVie designated laboratory outside of China for long term storage. All samples will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-493 and ABT-530 or drugs for the treatment of HCV continues but no longer than 5 years after completion of this study and all study endpoint data are analyzed.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of ABT-493, possible ABT-493 metabolites, ABT-530, possible ABT-530 metabolites and HIV-1 ART regimens will be collected by venipuncture at each study visit during the DB or OL Treatment Periods as indicated in Appendix C.

Subjects who do not participate in Optional Intensive PK sampling:

- At all DB and OL Treatment Period visits, except for Day 1, a single blood sample (3 mL) will be collected for ABT-493/ABT-530 without regard to the time of dosing. For co-infected subjects only, an additional blood sample (4 mL) will be collected for possible HIV-1 ART assays.
- The date and time of blood sample collection and the two previous doses of the study drug will be recorded to the nearest minute in the source documents. Additionally, the date and time of the two previous doses of the study drug will be recorded to the nearest minute on the eCRF.

Subjects who consent to participate in Optional Intensive PK sampling:

- On DB Day 1 and the DB and OL Week 4 visits, subjects will have their dose administered by study site personnel after food. Blood samples (3 mL each) will be collected on DB Day 1 at 2, 4 and 6 hours post-dose and at the DB and OL Week 4 Visits immediately prior to dose (0 hour) and 2 and 4 hours post-dose. For co-infected subjects only, an additional blood sample (4 mL) will be collected at each timepoint for possible HIV-1 ART assays.
  - The date and time of site-administered dose, blood sample collection and the two previous doses of study drug (for Week 4 Visit only) will be recorded to the nearest minute in the source documents. Additionally, the date and time of the site-administered dose and two previous doses (for Week 4 Visit only) will be recorded in the eCRF.
- At all other DB and OL Treatment Period visits, a single blood sample (3 mL) will be collected for ABT-493/ABT-530 without regard to the time of dosing. For co-infected subjects only, an additional blood sample (4 mL) will be collected for possible HIV-1 ART assays.
  - The date and time of blood sample collection and the two previous doses of the study drug will be recorded to the nearest minute in the source documents. Additionally, the date and time of the two previous doses of the study drug will be recorded to the nearest minute on the eCRF.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood samples and subsequent preparation and storage of the plasma samples for the pharmacokinetic assays of ABT-493 and ABT-530 (and their possible metabolites) and HIV-1 ART regimens will be provided by the central laboratory, AbbVie, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of ABT-493 and ABT-530 (and their possible metabolites), HIV-1 ART regimens and archive plasma samples will

be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

The central laboratory will then ship the ABT-493, ABT-530 and HIV-1 ART samples to the reference laboratories following separately provided instructions.

5.3.2.4 Measurement Methods

Plasma concentrations of ABT-493 and ABT-530 will be determined using validated assay methods under the supervision of the Drug Analysis Department at AbbVie. Plasma concentrations of possible metabolites of any analytes listed above may also be determined using either validated or non-validated methods.

Plasma concentrations of HIV-1 ART regimens for individual subjects, a group of subjects or for the whole study may be analyzed based on safety, HCV RNA and plasma HIV-1 RNA results. The plasma concentrations of HIV-1 ART regimens will be determined, if necessary, under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

HCV virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 24 weeks after completion or discontinuation of active treatment in either DB Treatment Period (Arm A) or the OL Treatment Period (Arm B).

5.3.3.1 Primary Variable

The primary efficacy variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) for the subjects treated with ABT-493/ABT-530 in the DB Treatment Period (Arm A).

5.3.3.2 Secondary Variables

The secondary efficacy variables are on-treatment HCV virologic failure and post-treatment relapse of HCV infection (excluding re-infection) in Arm A subjects, and SVR_{12} for HCV/HIV co-infected Arm A subjects.

5.3.4 HCV Resistance Variables

For all subjects receiving active study drugs who experience virologic failure, the HCV amino acid variants at signature resistance-associated positions in NS3 and NS5A at baseline identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving active study drugs who experience virologic failure and who have an available post baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the HCV amino acid variants in NS3 and NS5A identified by population or deep sequencing and comparison to the baseline sequence, 2) the HCV amino acid variants at signature resistance-associated amino acid positions in NS3 and NS5A identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence, and 3) the persistence of HCV viral amino acid variants in NS3 and NS5A by population or deep sequencing.

5.3.5 HIV Resistance Variables

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 integrase sequences may be analyzed as indicated by local standard of care practices.

5.3.6 Safety Variables

The following safety evaluations will be performed during the study: adverse events, vital signs, physical examination, ECG, and laboratory tests assessments.

HIV virologic response will be assessed by plasma HIV-1 RNA levels in copies/mL at various time points during the DB and OL Treatment Periods and the Post-Treatment Period.

5.3.7 Pharmacokinetic Variables

Individual plasma concentrations of ABT-493 and ABT-530 (and their possible metabolites) will be tabulated and summarized. Plasma concentrations of HIV-1 ARTs for individual subjects, a group of subjects or for the whole study may be analyzed based on HCV RNA and/or plasma HIV-1 RNA results and summarized.

5.3.8 Pharmacogenetic Variables

IL28B status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. These IL28B GT results may be analyzed as part of a multi-study assessment of IL28B and response to ABT-493, ABT-530, or drugs of these classes. The results may also be used for the development of diagnostic tests related to IL28B and study treatment, or drugs of these classes. The results of additional IL28B pharmacogenetic analyses may not be reported with the clinical study report.

DNA samples from subjects who separately consent for additional pharmacogenetic analysis may be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to study treatment, in terms of pharmacokinetics, efficacy, tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. Pharmacogenetic analyses will be limited to ABT-493 and ABT-530, drugs of this class, HCV and related conditions. Pharmacogenetic analyses will not be done to determine a subject's predisposition to unrelated diseases. Pharmacogenetic analyses will take place at an AbbVie designated laboratory in China and data will be exported to AbbVie in the United States.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

If, during the DB or OL Treatment Period, the subject prematurely discontinues, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Appendix C. Ideally this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment. The last dose of any study drug and reason for discontinuation will be recorded in the EDC (electronic data capture) system. The subject should then begin the Post-Treatment Period where the subject will be monitored for 24 weeks for HCV RNA, the emergence and/or persistence of resistant viral variants, plasma HIV-1 RNA, HIV resistance (as applicable) and PROs (Arm A Only).

Subjects prematurely discontinuing from the DB period and who on un-blinding are found to have been randomized to placebo may elect to remain in the study (at the investigator's discretion) and receive active treatment during the Open-Label Period. However, the subject is expected to continue to attend all remaining DB Treatment Period study visits and perform all remaining study procedures through the final scheduled DB visit (Week 8 or Week 16), in order to be eligible to enter the OL Treatment Period and receive active open-label treatment.

If a subject is discontinued from the Post Treatment Period, the subject should return for Post-Treatment Discontinuation procedures as defined in Appendix C. The reason for discontinuation will also be recorded in the Study Discontinuation eCRF.

If a subject is discontinued from study drug or the Post-Treatment Period with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the DB or OL Treatment Period, the administration of DAAs to that subject may be continued at the Principal Investigator's discretion after discussion with the subject, if the benefit of continuing DAAs is felt to outweigh the potential risk. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. Subjects will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.4.

5.4.1.1 HCV Virologic Stopping Criteria

During the DB Treatment Period of the study, the HCV virologic results will be reviewed and HCV virologic stopping criteria will be applied to those subjects randomized to active drugs by an un-blinded independent reviewer who will provide information to the investigators to assist with managing these subjects according to the criteria below. No HCV virologic stopping criteria will be applied to subjects randomized to placebo during the DB Treatment Period. During the OL Treatment Period, investigators will be un-blinded to HCV virologic data and will manage subjects according to the criteria below.

HCV virologic stopping criteria are defined as follows:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment; or

- Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during treatment.

When confirmatory testing is required it should be completed as soon as possible and the subject should remain on study treatment until the HCV virologic stopping criterion has been confirmed. Subjects meeting a virologic stopping criterion will be discontinued from study drug and will continue to be followed in the Post-Treatment Period for the emergence and persistence of resistant viral variants, plasma HIV-1 RNA, HIV resistance (as applicable) and PROs (Arm A only) until 24 weeks post-treatment.

5.4.1.2 Failure to Maintain HIV Virologic Suppression

HIV-1 RNA will be assessed at each scheduled study visit during the DB Treatment Period, OL Treatment Period and PT Period, as detailed in Appendix C.

For HCV/HIV-1 Co-Infected Subjects on Stable ART

The criteria for failure to maintain HIV virologic suppression is as follows:

- HIV-1 RNA ≥ 200 copies/mL confirmed on 2 consecutive tests at least 2 weeks apart, in a subject compliant with their HIV ART therapy.

At the time a confirmatory HIV-1 RNA is drawn, a sample for HIV-1 genotypic resistance testing may also be obtained; this sample may be analyzed if the subject's repeat plasma HIV-1 RNA is ≥ 500 copies/mL. A subject should remain on HCV study drug treatment and his/her current ART regimen while the failure to maintain HIV virologic suppression is being confirmed. A confirmatory HIV-1 RNA and HIV-1 genotypic resistance blood draw can be done as an unscheduled visit. However, if this blood draw falls on the date of a scheduled study visit (Appendix C), only a single HIV-1 RNA and HIV-1 genotypic resistance blood draw needs to be performed at this visit.

Clinical management of failure to maintain HIV-1 virologic suppression during the study (DB and OL Treatment Periods and Post-Treatment Period) will be handled by the site investigator according to current HIV treatment guidelines and local standard of care.

If the investigator wishes to change the HIV-1 ART regimen for a subject, it must be discussed with the AbbVie TA MD prior to the change being made, unless the change is being made to address an immediate safety concern.

During the DB or OL Treatment Periods, subjects with confirmed failure to maintain HIV-1 RNA suppression should continue study drug (active or matching placebo) treatment unless there is a requirement for prohibited concomitant medications (see Section 5.2.3.2 and Section 5.2.3.4) to construct a new HIV ART regimen.

For HCV/HIV-1 Co-Infected Subjects Naïve to ART

Clinical management of ART-naïve co-infected subjects during the study (DB and OL Treatment Periods and Post-Treatment period) will be handled by the site investigator according to current HIV treatment guidelines and local standard of care. During the DB and OL Treatment Periods, if an investigator deems it necessary to initiate HIV-1 ART for a subject, continuation of study drug treatment must be discussed with the AbbVie TA MD prior to ART initiation.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of blinded or open-label study drugs (ABT-493/ABT-530 or placebo) will be dispensed in the form of film-coated co-formulated tablets at the visits listed in Appendix C. Subjects will be instructed to take study drugs at the same time every day with food. Prior to all visits with pharmacokinetic sampling, the date and time of the two previous doses will be recorded to the nearest minute in the source documents and the eCRF. For subjects participating in Intensive PK sampling on Study Day 1 and at the Week 4 visit during the DB and OL treatment periods, they will have their dose administered by study site personnel after food and blood samples are collected for assay of study drugs. The date and time of dosing and blood sample collection will be recorded to the nearest minute in the source document.

In Arm A, ABT-493/ABT-530 will be provided by AbbVie as 100 mg/40 mg film-coated tablets. ABT-493/ABT-530 will be taken orally as 3 tablets QD with food, which corresponds to ABT-493 300 mg/ABT-530 120 mg QD.

In Arm B, placebo matching the ABT-493/530 will be provided by AbbVie.

Subjects in Arm B entering the OL Treatment Period will be given ABT-493/ABT-530 as 100/40 mg film-coated tablets to be taken orally as 3 tablets QD with food at the final scheduled DB Treatment Period visit (Week 8 or Week 16) along with instructions to begin dosing the next day. The site will call the subject within 4 days after the final scheduled DB Treatment Period visit to confirm dosing on OL Day 1 and record the date of the first dose in the source documents.

Study drugs (ABT-493/ABT-530 and matching placebo) should be taken with food.

Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the DB and OL Treatment Periods or at the Premature D/C Visit from the DB or OL

Treatment Period, the site will contact the IRT system to provide visit date information and study drug return information for each kit (Section 5.5.7).

All subjects who receive at least one dose of active study drug, either in the DB or OL Treatment Period, and meet the HCV virologic stopping criteria or fail to maintain HIV virologic suppression should follow instructions in Section 5.4.1.1 and Section 5.4.1.2, respectively.

5.5.2 Identity of Investigational Product

Information about the study drugs to be used in this study is presented in Table 3.

Table 3. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
ABT-493/ABT-530	AbbVie	Oral	Film Coated Tablet	100 mg/40 mg
Placebo for ABT-493/ABT-530	AbbVie	Oral	Film Coated Tablet	0 mg

5.5.2.1 Packaging and Labeling

All study drugs, including matching placebo, will be supplied in matching bottles.

Each bottle will be labeled as required per country requirements.

The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

5.5.2.2 Storage and Disposition of Study Drug

Study Drug	Storage Conditions
ABT-493/ABT-530 bottles	15° to 25°C (59° to 77°F)
Placebo for ABT-493/ABT-530	15° to 25°C (59° to 77°F)

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie.

5.5.3 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, all subjects will be assigned a unique subject number through the use of IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number, assigned at the Screening Visit, throughout the study. For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive unique randomization numbers. The randomization number will be used only by AbbVie for loading the treatment assignments into the database. The randomization numbers will be assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

Subjects meeting the eligibility criteria will be randomized as described in Section 8.3.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.4. Study drug dosing will be initiated at the DB Day 1 Visit.

All three tablets of ABT-493/ABT-530 or placebo will be dosed together QD. All subjects should take all doses of study medications with food.

Subjects initially randomized to placebo in the DB Treatment Period will begin open-label ABT-493/ABT-530 on OL Day 1, the day after the final scheduled DB Period visit (Week 8 or Week 16).

5.5.5 Blinding

Investigators, study site personnel, AbbVie, and subjects will remain blinded to each subject's treatment during the DB Treatment Period. ABT-493/ABT-530 and matching placebo will be provided as tablets.

During the DB Treatment Period, measures to prevent implicit un-blinding by laboratory results will be used. Specifically, the results of HCV RNA, ALT, AST, and bilirubin (indirect and total), will be blinded to the investigator, subject and AbbVie until the final scheduled DB Period visit (Week 8 or Week 16) or Premature D/C Visit, unless criteria for HCV virologic failure or relevant predefined toxicity are met, in which case the relevant laboratory data will be un-blinded to the investigator, subject and AbbVie, see Section 5.4.1.1, and Section 6.1.7. During the blinded period, an un-blinded independent reviewer will review HCV RNA data and provide guidance related to HCV virologic failure (Section 5.4.1.1).

A subject's study drug assignment may be un-blinded as part of toxicity management, at the investigator's or TA MD's discretion (if deemed necessary for subject safety), or at premature discontinuation. If a subject's treatment assignment is formally un-blinded during the DB Treatment Period then results of the previously blinded laboratory tests, i.e., HCV RNA levels, transaminases, and bilirubin (indirect and total) will be provided to the investigator and AbbVie.

In the setting of premature discontinuation of double-blind study drug for toxicity management or HCV virologic failure (for those subjects on active drug), the investigator, subject and AbbVie will be un-blinded to study drug assignment via IRT. Subjects

prematurely discontinuing and who on un-blinding are found to have been randomized to placebo may elect to remain in the study (at the Investigator's and the TA MD's joint decision) and receive active treatment during the Open-Label Period. However, the subject is expected to attend all remaining DB Treatment Period study visits and perform all remaining study procedures through the final scheduled DB Period visit (Week 8 or Week 16), in order to be eligible to enter the OL Treatment Period and receive active treatment. During the OL Treatment Period, open-label ABT-493/ABT-530 will be supplied. Subjects prematurely discontinuing and who on un-blinding are found to have been randomized to active study drugs will enter the PT Period at the time of discontinuation.

The IRT system will be programmed with blind-breaking capability. The study blind may be broken if, in the opinion of the investigator, it is in the subject's best interest to know the study drug assignment. The sponsor, AbbVie, MUST be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. If an emergency situation warrants breaking the blind, AbbVie must be notified within 24 hours of the blind being broken. The date and reason the blind was broken must be recorded in the source records and on the appropriate eCRF. The study blind may also be broken by the appropriately delegated AbbVie employees for safety and pharmacokinetic sample analysis reasons. Any employees of AbbVie who are un-blinded will not be involved in other aspects of the trial or its management.

5.5.5.1 Blinding of Investigational Product

In order to maintain the blind, the ABT-493/ABT-530 and placebo tablets provided for the study will be identical in appearance and will be supplied in matching bottles.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

At the start of the study, each subject should receive counseling regarding the importance of dosing adherence with the treatment regimen with regard to virologic response and potential development of resistance due to poor compliance.

At each study drug accountability visit during the DB and OL Treatment Periods (see Appendix C), subjects will be instructed to bring all bottles of study drug (full, partial or empty) for assessment of treatment compliance. At post-baseline dispensing visits denoted in Appendix C, study site personnel will assess subject compliance by inspecting the contents of the bottles and record the status of each one, as well as the exact number of remaining tablets of ABT-493/ABT-530 or placebo in IRT. Treatment compliance will be based on the number of tablets dispensed, as recorded in IRT, and the number of remaining tablets. If poor compliance is noted, the subject should be counseled and this should be documented in the subject's source.

5.5.7 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts via the IRT system. A current (running) and accurate inventory of study drug will be kept by the investigator and will include lot number, kit number, number of tablets dispensed, subject number, initials of person who dispensed study drug and date dispensed for each subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the DB and OL Treatment Periods. The monitor will review study drug accountability on an ongoing basis. Final accountability will be verified by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug bottle of ABT-493/ABT-530 or placebo, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the bottle is damaged, the subject will be requested to return the remaining study drug to the site. Replacement study drug may only be dispensed to the subject by contacting the IRT system. Study drug replacement(s) and an explanation of the reason for the misplaced or damaged study drug(s) will be documented

within the IRT system. Study drug start dates for each drug and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each bottle, number of tablets remaining in each one returned, and the date of reconciliation will be documented in the IRT system. The monitor will review study drug accountability on an ongoing basis.

Upon completion of or discontinuation from the DB or OL Treatment Period, all original study drug bottles (containing unused study drugs) will be returned to AbbVie (or designee) or destroyed on site. All destruction procedures will be according to instructions from AbbVie and according to local regulations following completion of drug accountability procedures. The number of tablets of each type of study drug returned in each bottle will be noted in the IRT system or on a drug accountability log (if appropriate). Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The selection of the treatment regimen is based on Phase 2 and Phase 3 studies which indicate that the combination of ABT-493/ABT-530 300/120 mg QD is generally safe and is optimal to achieve high SVR rates in HCV GT1 – 6 infected subjects.

The current study (Study M15-592) is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to evaluate the safety and efficacy of ABT-493/ABT-530 300/120 mg QD combination in treatment-naïve or treatment-experienced (i.e., alpha, beta or pegylated interferon [pegIFN]) with or without RBV OR sofosbuvir with RBV with or without IFN. HCV GT1 – 6 infected Asian adult subjects without cirrhosis, with or without HIV-co-infection. The treatment duration is 8 weeks in non-cirrhotic subjects, with the exception of treatment-experienced GT3 HCV non-cirrhotic subjects who will receive 16 weeks of treatment.

The Phase 2 and 3 Analysis Set (integrated) from the global clinical development program includes all subjects who received doses of ABT-493 300 mg QD and ABT-530 120 mg

QD either from registrational studies or in supportive Phase 2 studies. Efficacy data through Post-Treatment Week 12 for all subjects in the Phase 2 and 3 Analysis Set were included for the primary (SVR_{12}) and secondary (on-treatment virologic failure and post-treatment relapse) endpoints. The Phase 2 and 3 Analysis Set organized by subject population is displayed in Table 4. Subjects were considered treatment-experienced if they had failed regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir (TE-PRS).

Table 4. Overview of Clinical Studies by Subject Population (Phase 2 and 3 Analysis Set)

Genotype	Clinical Study	Summary of Study Design
TN and TE Subjects Without Cirrhosis		
GT1	M13-590*	ABT-493/ABT-530 300 mg/120 mg QD for 8 (n = 351) or 12 weeks (n = 352)
	M14-867	ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks (n = 34)
GT2	M15-464	ABT-493/ABT-530 300 mg/120 mg QD (n = 202) or placebo (n = 100) for 12 weeks
	M14-868	ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks (n = 199) or 12 weeks (n = 25)
GT3	M13-594	ABT-493/ABT-530 300 mg/120 mg QD for 8 (n = 157) or 12 weeks (n = 233) or SOF 400 mg + DCV 60 mg QD for 12 weeks (n = 115) (all subjects in study were TN)
	M14-868	ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks (n = 29; TN only), 12 weeks (n = 76), or 16 weeks (n = 22; TE only)
GT4, GT5, GT6	M13-583	ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks (n = 121)
	M14-867	ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks (n = 32)
	M14-868	ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks (n = 58)
TN and TE Subjects With Cirrhosis		
GT1, GT2, GT4, GT5, GT6	M14-172	ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks (n = 146)
GT3	M14-868	ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks (n = 64; TN only) or 16 weeks (n = 51; TE only)
Subjects With CKD Stages 4 – 5 With or Without Cirrhosis		
GT1 – GT6	M15-462	ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks (n = 104)
NS5A Inhibitor and/or PI-Experienced Subjects With or Without Cirrhosis		
GT1, GT4	M15-410	ABT-493/ABT-530 300 mg/120 mg QD for 12 (n = 66) or 16 weeks (n = 47)

CKD = chronic kidney disease; DCV = daclatasvir; GT = genotype; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; QD = once daily; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naïve

* HCV monoinfected or HIV-coinfected.

Treatment durations were selected based on Phase 2 and 3 Analysis Set from 8-week or 12-week treatment groups receiving ABT-493/ABT-530 300/120 mg combinations in HCV GT1, GT2, GT3, GT4, GT5, and GT6-infected non-cirrhotic patients with or without previous treatment experience (Table 5, Table 6, and Table 7).

Table 5. Summary of SVR_{12}, On-Treatment Virologic Failure, and Post-Treatment Relapse in TN and TE Non-GT3-Infected Subjects by Cirrhosis Status (TN + TE-PRS Subjects, Phase 2 and 3 Analysis Set)

	n/N (%)														
	GT1			GT2			GT4			GT5			GT6		
Endpoint	8 Weeks	12 Weeks	Overall	8 Weeks	12 Weeks	Overall	8 Weeks	12 Weeks	Overall	8 Weeks	12 Weeks	Overall	8 Weeks	12 Weeks	Overall
Subjects Without Cirrhosis															
SVR_{12}	383/387 (99.0)	400/401 (99.8)	783/788 (99.4)	193/197 (98.0)	232/234 (99.1)	425/431 (98.6)	43/46 (93.5)	111/112 (99.1)	154/158 (97.5)	2/2 (100)	28/28 (100)	30/30 (100)	9/10 (90.0)	31/31 (100)	40/41 (97.6)
OTVF	1/387 (0.3)	0/401	1/788 (0.1)	0/197	0/234	0/431	0/46	0/112	0/158	0/2	0/28	0/30	0/10	0/31	0/41
$Relapse_{12}$	0/384	0/400	0/784	2/195 (1.0)	0/232	2/427 (0.5)	0/45	0/111	0/156	0/2	0/27	0/29	0/10	0/30	0/40
Subjects With Cirrhosis															
SVR_{12}	N/A	98/101 (97.0)	98/101 (97.0)	N/A	35/35 (100)	35/35 (100)	N/A	20/20 (100)	20/20 (100)	N/A	2/2 (100)	2/2 (100)	N/A	7/7 (100)	7/7 (100)
OTVF	N/A	0/101	0/101	N/A	0/35	0/35	N/A	0/20	0/20	N/A	0/2	0/2	N/A	0/7	0/7
$Relapse_{12}$	N/A	1/98 (1.0)	1/98 (1.0)	N/A	0/35	0/35	N/A	0/19	0/19	N/A	0/2	0/2	N/A	0/7	0/7

GT = genotype; HCV = hepatitis C virus; N/A = not applicable; OTVF = on-treatment virologic failure; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; $Relapse_{12}$ = relapse before or during the SVR_{12} window; RNA = ribonucleic acid; SVR_{12} = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naïve

Table 6. SVR_{12} Rates by Prior Treatment Experience, HCV Genotype, and Duration for Non-GT3 Infected Subjects (ITT Population, Phase 2 and 3 Analysis Set)

Treatment Group	n/N (%)									
	GT1		GT2		GT4		GT5		GT6	
	8 Weeks	12 Weeks	8 Weeks	12 Weeks	8 Weeks	12 Weeks	8 Weeks	12 Weeks	8 Weeks	12 Weeks
TN	245/248 (98.8)	310/313 (99.0)	172/174 (98.9)	193/195 (99.0)	36/39 (92.3)	83/83 (100)	2/2 (100)	24/24 (100)	7/8 (87.5)	33/33 (100)
TE-PRS	138/139 (99.3)	188/189 (99.5)	21/23 (91.3)	74/74 (100)	7/7 (100)	48/49 (98.0)	N/A	6/6 (100)	2/2 (100)	5/5 (100)
TN + TE-PRS										
All	383/387 (99.0)	498/502 (99.2)	193/197 (98.0)	267/269 (99.3)	43/46 (93.5)	131/132 (99.2)	2/2 (100)	30/30 (100)	9/10 (90.0)	38/38 (100)
% Difference (8-week – 12 week) 95% CI	–0.7 (–2.1, 0.6)		–1.4 (–4.4, 1.7)		–5.6 (–14.1, 2.9)		0.0 (–73.3, 73.3)		–10.5 (–37.8, 16.9)	

CI = confidence interval; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat (all subjects who received at least 1 dose of study drug); N/A = not applicable; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SVR_{12} = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naïve

Table 7. Summary of SVR_{12}, On-Treatment Virologic Failure, and Post-Treatment Relapse in TN and TE GT3-Infected Subjects by Cirrhosis Status and Treatment Duration (ITT Population, Phase 2 and 3 Analysis Set)

	n/N (%)			
	TN		TE-PRS	
Endpoint	**8 Weeks**	**12 Weeks**	**12 Weeks**	**16 Weeks**
Subjects Without Cirrhosis				
SVR_{12}	177/186 (95.2)	258/270 (95.6)	44/49 (89.8)	21/22 (95.5)
OTVF	1/186 (0.5)	1/270 (0.4)	1/49 (2.0)	0/22
$Relapse_{12}$	5/178 (2.8)	3/257 (1.2)	4/48 (8.3)	1/22 (4.5)
Subjects With Cirrhosis				
SVR_{12}	N/A	64/65 (98.5)	N/A	48/51 (94.1)
OTVF	N/A	0/65	N/A	1/51 (2.0)
$Relapse_{12}$	N/A	0/64	N/A	2/50 (4.0)

GT = genotype; ITT = intention-to-treat (all subjects who received at least 1 dose of study drug); N/A = not applicable; OTVF = on-treatment virologic failure; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; $Relapse_{12}$ = relapse before or during the SVR_{12} window; SVR_{12} = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naïve

Treatment-experienced GT3-infected subjects with and without cirrhosis were evaluated for 12-week and 16-week durations of treatment. Among TE GT3-infected subjects without cirrhosis, the SVR_{12} rates were higher in subjects treated for 16 weeks (95.5%) compared to 12 weeks (89.8%). Subjects with cirrhosis treated for 16 weeks achieved a high (94.1%) SVR_{12} rate, similar to subjects without cirrhosis (95.5%). These results in GT3-infected subjects support the use of 16 weeks of treatment in TE GT3-infected subjects with or without cirrhosis.

Based on the efficacy data presented above, the 8-week treatment duration is anticipated to achieve high SVR rates in GT 1, 2, 3, 4, 5 and 6 infected treatment-naïve and -experienced subjects without cirrhosis, with the exception of 16 weeks for treatment-experienced GT3-infected subjects as depicted in Table 8.

Table 8. Recommended Treatment Duration for Subjects Without Cirrhosis

Patient Population	Recommended Treatment Duration
Treatment-naïve	8 weeks
Treatment-Experienced*	8 weeks (16 weeks for GT 3)

* Treatment-experienced to interferon (IFN) (alpha, beta or pegylated interferon [pegIFN]) with or without ribavirin (RBV) OR sofosbuvir with RBV with or without IFN.

As SVR rates for the current therapies (e.g., ombitasvir/paritaprevir/ritonavir ± RBV or sofosbuvir/ledispavir) in non-cirrhotic subjects are well-established and very high (≥ 95%) in various GTs, historical control data will be used to provide a comparator for assessment of efficacy in this placebo-controlled study.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA and HIV-1 RNA assays are standard and validated.

5.6.3 Suitability of Subject Population

This study plans to enroll HCV GT1, 2, 3, 4, 5, and 6-infected subjects without cirrhosis who are treatment-naïve or treatment-experienced to prior HCV therapy with or without HIV co-infection in order to assess the safety, pharmacokinetics and antiviral activity of ABT-493/ABT-530. Subjects who are treatment-naïve as well as those who received prior treatment with IFN (alpha, beta or pegylated interferon [pegIFN]) with or without RBV OR sofosbuvir with RBV with or without IFN for their HCV infection are included in the study in order to evaluate the efficacy of ABT-493/ABT-530 regimen in this diverse cohort of HCV GT1 – 6-infected subjects. Subjects who have failed treatment with a PI or NS5A inhibitor alone or in combination with interferon (with or without RBV) will not be permitted to enroll.

HCV-infected subjects who are on stable opiate (methadone or buprenorphine/naloxone) maintenance therapy will be allowed to enroll in this study based on the results from Study M13-602 evaluating the pharmacokinetic, pharmacodynamic, safety and tolerability effects of the coadministration of buprenorphine/naloxone or methadone and the DAAs (ABT-493 + ABT-530) in adult subjects on stable opioid maintenance therapy showing acceptable safety and no relevant pharmacokinetic or pharmacodynamic interactions.

5.6.4 Selection of Doses in the Study

5.6.4.1 Rationale for Dose Selections

The doses of 300 mg ABT-493 and 120 mg ABT-530 were selected to optimize efficacy of the combination while maintaining an acceptable safety profile.

5.6.4.1.1 ABT-493 and ABT-530 Doses

Based on the results from the Phase 2b studies, Studies M14-867 and M14-868, the 300 mg dose of ABT-493 and 120 mg dose of ABT-530 in combination has been selected for Phase 3 studies in HCV GT1 to 6 cirrhotic and non-cirrhotic populations and is also applicable for this Asian regional Phase 3 study. This dose has been demonstrated efficacious for the proposed Phase 3 study populations with the planned study duration

and would reduce the chance of virologic failure across genotypes and difficult-to-treat patient populations to maximize the chance for SVR. Importantly, ABT-493 and ABT-530 regimens including the proposed 300 mg/120 mg ABT-493/ABT-530 QD regimen have been well-tolerated and safe across all Phase 2b study arms including cirrhotic subjects.

Further detailed rationale is provided below:

- In Phase 1 studies, no ethnic difference was observed in ABT-493 and ABT-530 exposures for, Han Chinese, Japanese and Caucasian subjects living in the United States.
- Based on in vitro studies, both ABT-493 and ABT-530 demonstrated strong pan-genotypic anti-viral activity. Given the potent in vitro efficacy across GTs and high SVR rates of 93% – 100% observed to date across dose groups in Phase 2 studies in GT1, GT2 and GT3-infected non-cirrhotic patients, the ABT-493/ABT-530 dose of 300 mg/120 mg are is expected to provide sufficient exposure to achieve significant antiviral potency in GT1-, GT2-, GT3-, GT4-, GT5- and GT6-infected non-cirrhotic subjects.
- Maximization of SVR rate: The ABT-493/ABT-530 combination has demonstrated SVR close to 100% in GT1 infected non-cirrhotic subjects with 12-week treatment duration in Part 1 of Study M14-867. All subjects in the 120 mg ABT-530 arm achieved SVR_{12}. However, one subject in the 40 mg ABT-530 Arm had virologic relapse when coadministered with the same dose of 200 mg ABT-493. Preliminary sequencing results indicate that the relapse subject developed treatment-emergent resistance associated substitutions in NS5A but not in NS3. These results suggest that the 120 mg ABT-530 dose may decrease the incidence of relapse by reducing the emergence of NS5A RAVs and thus increase the chance of achieving SVR compared to 40 mg.
- For GT2 and GT3 subjects, ABT-493 doses of 200 mg and 300 mg were evaluated in Part 1 of Study M14-868. No virological breakthroughs and no relapses were observed in subjects with GT2 infection at either of the 2 ABT-493 dose levels. For GT3 arms, 2 subjects (1 TN and 1 PR-experienced) had virological breakthrough before the completion of treatment in the 200 mg ABT-493 groups. No subjects receiving 300 mg ABT-493 have

had breakthroughs before completion of treatment. The results suggested that the 300 mg ABT-493 dose reduces the incidence of breakthroughs and increases the chance of achieving SVR. Taken together, these data suggest that ABT-493/ABT-530 dose of 300/120 will maximize SVR rate compared to lower dose-combinations.

- For other genotypes (GT4, 5 and 6), the 300 mg/120 mg ABT-493/ABT-530 combination for 12 weeks achieved 100% SVR_4.
- ABT-493 and ABT-530 regimens including the proposed 300 mg/120 mg ABT-493/ABT-530 QD regimen have been well-tolerated and safe across all Phase 2b study arms including cirrhotic subjects. All ABT-493 and ABT-530 doses studied had a similar safety profile. The most frequently reported adverse events were fatigue, nausea and headache and were mostly Grade 1 or 2 in severity. In all subjects with baseline ALT elevations, the ALT levels have normalized or trended toward normal with DAA treatment, and there have been no on treatment ALT elevations above baseline grade.
- Based on the integrated pharmacokinetic exposures of ABT-493 and safety data in healthy subjects across 100 mg to 1200 mg dose range, ALT elevations ≥ Grade 2 are only anticipated to occur when ABT-493 AUC is higher than 190,000 ng•h/mL, which is 33× higher than the projected geometric mean AUC exposure at ABT-493 300 mg in non-cirrhotic subjects.
- ABT-530 had shown to be safe and well tolerated at 600 mg QD multiple dosing and MTD was not achieved. Although ABT-493 300 mg increases ABT-530 exposure at 120 mg by 4-fold, the increased ABT-530 exposure was still less than the exposures of ABT-530 600 mg QD in Study M13-356 and no significant safety signal was observed in healthy subjects and HCV infected patients. No clinically meaningful adverse events or laboratory abnormalities were observed in any ABT-530 120 mg dose groups in Phase 2 Studies M14-867 and M14-868.
- For HIV-HCV co-infected patients, extensive drug-drug interaction studies have been conducted between HIV-1 ART regimens and ABT-493 + ABT-530 combinations. The allowed HIV-1 ART regimens in the study are not anticipated to significantly interact with ABT-493 and ABT-530.

- A film-coated co-formulated bilayer tablet of ABT-493 and ABT-530 will be used in this Phase 3 study. Preliminary pharmacokinetic results of the Phase 3 [redacted] bilayer tablet formulation administered under fasting conditions showed approximately 35% to 56% lower bioavailability compared to the Phase 2 formulations at the ABT-493/ABT-530 dose of 300 mg/120 mg. When the Phase 3 bilayer tablet was administered under non-fasting conditions, exposures became comparable to the Phase 2 formulation. Hence, the Phase 3 co-formulated ABT-493/ABT-530 bilayer tablet must be administered with food to provide desirable DAA exposures.

The maximum dose of ABT-493/ABT-530 will not exceed 300 mg/120 mg per day for 8 or 16 weeks.

5.6.4.2 Rationale for Duration Selections

Treatment duration for this Asian regional Phase 3 study was determined based on study results from the Global program. The treatment duration differs among subjects based on HCV GT and treatment experience (8 weeks of treatment for treatment-naïve and treatment-experienced GT1, 2, 3, 4, 5 and 6-infected subjects with the exception of 16 weeks for treatment-experienced GT3-infected subjects).

Results from ABT-493 300 mg QD + ABT-530 120 mg QD for an 8-week treatment duration in HCV GT1- (Study M14-867 Part 2) and HCV GT2-infected subjects (Study M14-867 Part 2) showed 100% SVR_{12}. In Study M14-867 Part 2, ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks was evaluated in 34 DAA-naïve HCV GT4 (n = 22), GT5 (n = 1), and GT6 (n = 11)-infected non-cirrhotic subjects. All 34 subjects achieved SVR_{12}. Based on exposure-response analyses, simulations were conducted to predict SVR rates for ABT-493 and ABT-530 administered for 8 weeks in HCV GT4-infected subjects and showed > 95% SVR in this population.

Treatment-naïve HCV GT3-infected subjects treated for 12 weeks achieved high efficacy (SVR_{12} rate of 98%) with no virological failures observed. Treatment-experienced HCV GT3-infected subjects with cirrhosis treated for 16 weeks achieved SVR_{12} rate of 96%,

with a low rate of relapse (2%). Among treatment-experienced subjects without cirrhosis, the 16-week regimen appeared to have a slightly higher SVR_{12} rate (96%) and a slightly lower relapse rate (5%) than the 12-week regimen. Treatment with the shorter duration of 12 weeks resulted in a slightly lower SVR_{12} rate (91%) and a slightly higher relapse rate (9%) compared to the 16 week regimen. There was a comparable safety profile for GT3 treatment-experienced subjects regardless of duration of treatment with study drug (12 or 16 weeks) and between subjects with or without cirrhosis.

Overall, the SVR_{12} rates for the GT3-infected treatment-experienced cohort, with and without cirrhosis, in the 16-week arm (SVR_{12} of 96% [66/69]) demonstrates that 16 weeks of treatment maximizes efficacy and is the most appropriate duration for this hardest-to-treat population.

5.6.4.3 Risk of Development of Resistance Mutations During Combination DAA Trials

In subjects treated with a DAA, variants with amino acid substitution(s) in the targeted protein conferring resistance to the DAA can be selected. For example, in AbbVie HCV Phase 3 studies in which patients with GT1 infection were treated with the NS3/4A protease inhibitor paritaprevir and NS5A inhibitor ombitasvir, variants that conferred resistance to paritaprevir or ombitasvir were detected in patients experiencing virologic failure. While resistance data from patients treated with the combination of ABT-530 and ABT-493 are limited, it is expected that ABT-530, an NS5A inhibitor, will be able to suppress the appearance of virus containing resistance-associated substitutions in NS3 that confer resistance to ABT-493, because there should not be any cross-resistance in variants resistant to DAAs targeting different proteins. The converse is expected to be true as well – ABT-493 should be able to suppress the appearance of virus containing NS5A variants conferring resistance to ABT-530. In addition, in vitro resistant colony selection studies in HCV replicon cells containing GT1 – 6 NS5A demonstrated that ABT-530 had a high genetic barrier to resistance – very few colonies were selected, and those that were selected contained NS5A variants that conferred only modest levels of resistance to ABT-530. It remains to be seen whether the development of resistance in subjects treated

with ABT-530 resembles that seen in vitro. Based on accumulated clinical and in vitro data to date, the risk of development of resistant variants during ABT-493 and ABT-530 combination trials is reduced when compared to treatment with first generation protease and NS5A inhibitors. For example, the combination of ABT-493 and ABT-530 achieved high SVR rates with few virologic failures in DAA-naïve patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection in the Phase 3 registrational studies. These results support the prediction that the risk of development of resistance-associated substitutions with ABT-493 and ABT-530 combination treatment is low.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to AbbVie (Section 6.2.2). For adverse events, please refer to Section 6.1 through 6.1.8. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 6.1.7 regarding toxicity management), and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the SAE.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4).

The table of clinical toxicity grades "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is available from the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf and is to be used in the grading of AEs. Below are the general grading categories. However, the investigator should always search NCI CTCAE for a given diagnostic/symptomatic AE term to identify and apply specific grading details for that AE entity.

Grading system for AEs (a semi-colon indicates 'or' within the description of the grade).

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

ADL = Activities of Daily Living

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	An AE where there is evidence to suggest a causal relationship between the study drug and the AE.
No Reasonable Possibility	An AE where there is no evidence to suggest a causal relationship between the study drug and the AE.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

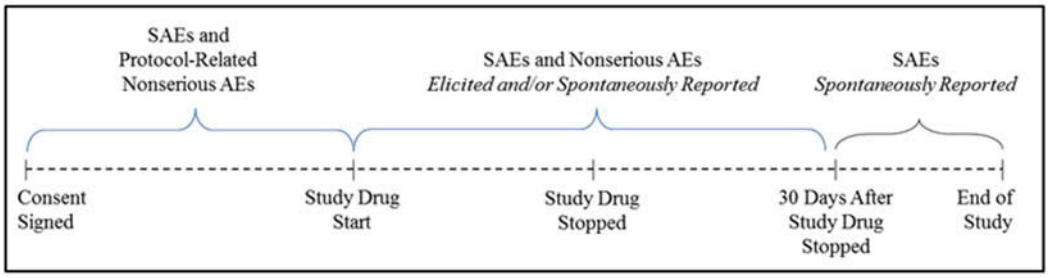
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of the event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All SAEs as well as protocol-related nonserious AEs (e.g., infection at liver biopsy site) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days following discontinuation of study treatment has elapsed, all AEs will be collected, whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment, and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of an SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Antiviral Safety Team at:

Antiviral Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Fax:
Email:

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

In emergency situations involving study subjects when the primary TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: 

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Female subjects who report a positive pregnancy test during the DB or OL Treatment Period may be continued at the investigator's discretion after discussion with the subject, if the benefits of continuing therapy are felt to outweigh the risk (Section 5.4.1). Subjects who discontinued and received active drug either in the DB or OL Treatment Period will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.4.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for pregnancies occurring up to 30 days after the end of treatment.

Pregnancy in a study subject is not considered an AE. However, the medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, stillbirth or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

For the purpose of medical management, all AEs and laboratory abnormalities that occur during the study must be evaluated by the investigator. All AEs and laboratory abnormalities will be managed and followed to a satisfactory clinical resolution. A toxicity is deemed "clinically significant" based on the medical judgment of the investigator. The table of clinical toxicity grades "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is to be used in the grading of AEs and laboratory abnormalities and is available on the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Specific toxicity management guidelines apply to the instances of increases in ALT (Section 6.1.7.1).

6.1.7.1 Management of Increases in ALT

If a subject experiences a post-baseline increase in ALT to > 5 × ULN which is also > 2 × the baseline value, the subject should have a confirmatory ALT measurement performed.

If the ALT increase is confirmed to be > 5 × ULN which is also 2 × the baseline value, the recommendations below should be followed:

- Complete hepatic questionnaire; evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate (e.g., hepatitis B panel, etc.).
- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs if any of the following is observed at any time:
  - ALT level is ≥ 20 × ULN in the absence of an alternate etiology.
  - Increasing direct bilirubin or INR or onset of symptoms/signs of hepatitis.
  - At the discretion of the investigator.

Alternate management of ALT increases is permitted with approval of the AbbVie TA MD.

During the DB Treatment Period, if confirmed ALT values meet or exceed predefined toxicity thresholds, refer to Section 5.1.2.

6.1.8 Collection of Data Regarding Known AIDS-Associated Opportunistic Infections

HIV-1 infected subjects participating in clinical trials may develop infections typically associated with AIDS. Appendix D contains a list of these known AIDS-associated opportunistic infections (OI). The events listed in Appendix D will be summarized as HIV-related events, not as AEs. These OIs will be collected from the time of study drug administration until 30 days following discontinuation of study drug.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to AbbVie within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to AbbVie (or an authorized representative) and documented in source as required by AbbVie. Product Complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying

Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), their assigned Site Monitor and the following AbbVie Clinical Team Members:

Primary Contact:	Alternate Contact:
[redacted]	

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

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. Data collected after this lock will be added to a new version of the database which will be cleaned and locked at the end of the study.

SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. All statistical tests and confidence intervals will be two-sided with an alpha level of 0.05. Descriptive statistics will be provided, such as the number of observations (N), mean, and standard deviation (SD) for continuous variables and counts and percentages for categorical variables.

Analyses will be performed on the intent-to-treat (ITT) population defined as all randomized subjects who receive at least one dose of study drug in the DB Treatment Period, unless otherwise specified. The primary and secondary efficacy endpoints will be analyzed on the ITT population treated with active study drug in the DB Treatment Period (Arm A). Sensitivity analyses of the primary efficacy endpoint, when applicable, will be performed on the ITT population modified to exclude subjects of multiple GTs according to the central laboratory or phylogenetic analyses (mITT-GT), and on the mITT-GT population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-VF). In addition, some analyses will be performed on the OL Population defined as all subjects who receive at least one dose of study drug during the OL Treatment Period.

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data), and PRO questionnaires. HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR_4, SVR_{12}, and SVR_{24}) based on defined visit windows. A backward imputation method will be used to impute missing responses for SVR analyses. Imputation of missing responses on PRO questionnaires is described in Section 8.1.3.

8.1.1 Demographics

DB Treatment Period

Demographics, baseline characteristics, study drug exposure, and compliance will be summarized by treatment arm for the set of all subjects in the ITT and mITT population(s) and for each of the GT1-infected and GT2-infected groups. Demographics include age (continuous; < 65 or ≥ 65 years; < 75 or ≥ 75 years), weight, height, waist circumference, BMI (continuous; < 25, ≥ 25 to < 30, or ≥ 30 kg/m^2), sex, race, ethnicity, type of Asian descent, and geographic region. Baseline characteristics will be summarized as continuous variables (where appropriate) and as categorical variables, including all subgroup variables defined in Section 8.1.2.4, and include HCV GT and available subtype, prior HCV treatment history, baseline HIV co-infection status, HIV ART at baseline, IL28B genotype (CC, CT, or TT; CC or non-CC), baseline HCV RNA level, baseline homeostasis model of assessment – insulin resistance (HOMA-IR), fibrosis stage (F0 – F1, F2, F3, F4 [if applicable]), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, injection drug user, (yes, within last 12 months; yes, more than 12 months ago; or no) use of stable opiate substitution, history of diabetes, baseline metabolic syndrome, history of bleeding disorders, history of depression or bipolar disorder, history of cardiovascular disease, and use of hepatoprotectants at baseline.

Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI), and the number and percentage of subjects will be presented for categorical variables (e.g., sex and race). Treatment arms will be compared using a chi-square test for categorical variables and using a one-way analysis of variance (ANOVA) with treatment arm as the factor for continuous variables.

Study drug exposure and compliance during the DB Treatment Period will be summarized. Treatment compliance to study drug will be calculated based on the percentage of tablets taken relative to the total tablets expected to be taken. A subject will be considered compliant if the percentage is between 80% and 120%. Compliance will be

calculated for each subject and summarized by treatment arm with the mean, median, standard deviation, minimum, and maximum. The percentage of compliant subjects will be calculated for 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 also be performed for each geographic region.

OL Treatment Period

Demographics, baseline characteristics, study drug exposure, and compliance 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. Summary statistics will be presented for continuous variables and the number and percentage of subjects will be presented for categorical variables.

Study drug exposure and compliance for the OL Population during the OL Treatment Period will be summarized using methods similar to those used for the DB Treatment Period.

The summaries described above will also be performed for each geographic region.

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population, unless otherwise specified.

Plasma HCV RNA levels will be determined by an approved HCV RNA quantitative assay for each sample collected by the central laboratory (including but not limited to Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0).

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) for the subjects treated with ABT-493/ABT-530 in the DB Treatment Period (Arm A). In order to control the Type I error rate, a fixed sequence

testing procedure will be used for the ranked primary efficacy endpoints. 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.

The three ranked primary efficacy endpoints are:

1. The percentage of Arm A subjects from the combined group of GT1 to 6-infected subjects 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% confidence interval (CI) for the percentage is > 90%.
2. The percentage of Arm A subjects from the group of GT1-infected subjects 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 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.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- the percentage of Arm A subjects with on-treatment HCV virologic failure (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ

during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and

- the percentage of Arm A subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment, excluding re-infection), and
- the percentage of Arm A HCV/HIV co-infected subjects (determined at Screening) achieving SVR_{12}.

For the analysis of relapse, a subject enrolled to receive 8 weeks of treatment is considered to have completed treatment if study drug duration is 52 days or more, and a subject enrolled to receive 16 weeks of treatment is considered to have completed treatment if study drug duration is 105 days or more.

The percentages of subjects with on-treatment HCV virologic failure, post-treatment relapse, and SVR_{12} will be calculated along with two-sided 95% Wilson score confidence intervals.

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

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.

8.1.2.3 Sensitivity Analysis

The analyses of the primary endpoints will also be performed on Arm A of the mITT-GT and mITT-GT-VF populations. Comparisons of the SVR_{12} rates may also be made to geographic region-specific SVR rates.

The number and percentage of subjects with SVR_{12} and the corresponding 95% confidence interval 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

8.1.2.4 Subgroup Analysis

The percentage of Arm A subjects with SVR_{12} will be calculated, as will the corresponding two-sided 95% Wilson score CIs, for subgroups based on the following factors for the set of all subjects in the ITT and mITT population(s) and for each of the GT1-infected and GT2-infected groups:

- Geographic region;
- HCV genotype and available subtype;
- Prior HCV treatment history;
- For treatment-experienced subjects, type of prior treatment experience;
- For treatment-experienced subjects, type of non-response to previous treatment;

- Baseline HIV co-infection status;
- IL28B genotype;
- Sex;
- Age;
- Type of Asian descent;
- Baseline BMI;
- Baseline HCV RNA level;
- Baseline HOMA-IR;
- Baseline fibrosis stage;
- Baseline platelet count;
- Baseline albumin;
- Baseline GGT;
- Baseline LDL;
- Baseline APRI;
- Baseline FIB-4;
- Baseline AST/ALT ratio;
- History of diabetes;
- History of bleeding disorders;
- History of depression or bipolar disorder;
- Baseline metabolic syndrome;
- History of cardiovascular disease;
- Injection drug use;
- Baseline stable opiate substitution use;
- Baseline hepatoprotectant medication use;
- Study drug compliance.

Further details about subgroup analyses will be described in the Statistical Analysis Plan (SAP).

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized for the set of all Arm A subjects in the ITT and mITT population(s) and for each of the GT1-infected and GT2-infected groups:

- 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 reason for SVR_4 non-response (e.g., on-treatment virologic failure, relapse, re-infection);
- 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);
- The percentage of subjects who relapsed after achieving SVR_{12}.

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:

- The percentage of subjects with SVR_{12};
- A summary of reason for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, other);
- The percentage of subjects with SVR_{12} by HCV genotype and available subtype;
- The percentage of subjects with SVR_{12} by HIV co-infection status;
- 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_{24};
- A summary of reason for SVR_{24} non-response (e.g., on-treatment virologic failure, relapse, re-infection);

- The percentage of subjects who relapsed after achieving SVR_{12};
- 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).

In the above analyses for SVR and relapse, the 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. The summaries listed above will also be presented by geographic region.

Additionally, the secondary endpoints will be summarized by geographic region, and the subgroup and sensitivity analyses will be performed separately for each geographic region.

The additional endpoints along with the secondary endpoints of on-treatment virologic failure and post-treatment relapse will also be summarized for the HCV/HIV co-infected subjects. The sensitivity analyses will also be performed for the HCV/HIV co-infected population.

8.1.3 Patient Reported Outcomes

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.

The mean change from baseline will be summarized descriptively for the FSS total score and the EQ-5D-3L health index score and VAS score for each treatment arm. 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 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 will also be calculated for each treatment arm.

The analyses described above will also be performed separately for each geographic region. Additional analyses of PROs will be performed as useful and appropriate.

8.1.4 HCV and HIV Resistance Analyses

For subjects who, experience HCV virologic failure (on treatment virologic failure or post-treatment relapse), full length NS3/4A and NS5A genes from their available baseline samples will be sequenced by population or deep sequencing. For each DAA target, resistance associated signature amino acid variants will be identified by AbbVie Clinical Virology. An appropriate prototypic reference sequence will be used for comparison with sequences from samples.

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 available 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 by either population or deep sequencing at the time of failure/discontinuation.

The following definitions will be used in the HCV resistance analyses:

- Baseline variant: a variant (by population or deep sequencing) in a baseline sample determined by comparison of the amino acid sequence of the baseline

sample to the appropriate prototypic reference amino acid sequence for a given DAA target.

- Post-baseline variant by population or deep sequencing: an amino acid variant detected by population or deep sequencing in a post-baseline time point sample that was not detected by population or deep sequencing at baseline in the subject.
- Emerged variant by population or deep sequencing: a post-baseline variant that is observed in 2 or more subjects of the same HCV subgenotype by population or deep sequencing.

The following analyses will be performed for all subjects in Arm A who experience virologic failure and for subjects in Arm B who experience virologic failure during or after the OL Treatment Period:

The HCV amino acid sequence as determined by population or deep sequencing of available baseline samples will be compared to the appropriate prototypic reference amino acid sequence. A listing by subject of all baseline variants relative to prototypic reference sequence at signature resistance associated amino acid positions will be provided for each DAA target (NS3 and NS5A).

The following analyses will be performed for subjects who experience virologic failure and have post-baseline resistance data available:

The HCV amino acid sequence as determined by population or deep sequencing on the sample closest in time after virologic failure with an HCV RNA level of $\geq$ 1000 IU/mL will be compared to the baseline and appropriate prototypic reference amino acid sequence. Listings by subject of all post-baseline amino acid variants detected by population or deep sequencing relative to the baseline amino acid sequences will be provided for each DAA target (NS3 and NS5A). Listings by subject of all emerged variants by population or deep sequencing, by amino acid position and variants within a DAA target in a post baseline sample relative to the baseline amino acid sequence will be provided for each DAA target. In addition,

listings by subject of all post-baseline amino acid variants (by population or deep sequencing) at signature resistance-associated positions relative to the appropriate prototypic reference amino acid sequence will be provided for each DAA target (NS3 and NS5A).

The persistence of post-baseline variants at signature resistance-associated amino acid positions for each target (NS3 and NS5A) will be assessed by population or deep sequencing at Post-Treatment Week 24. Listings by subject and time point of all post-baseline variants relative to the baseline amino acid sequence will be provided for each DAA target (NS3 and NS5A).

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

HIV-1 drug resistance genotyping for protease, reverse transcriptase and integrase sequences may be performed for protocol-defined eligible specimens.

8.1.5 Safety

All subjects who receive at least one dose of study drug will be included in the safety analyses. Safety data will be summarized for the set of all subjects and for each of the GT1-infected and GT2-infected groups; these summaries will also be performed separately for each geographic region. Safety data will also be summarized for the set of HCV/HIV co-infected subjects. 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. The data from the OL Treatment Period and PT Period will also be summarized, but no comparisons will be performed.

8.1.5.1 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AE data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms according to the version of the MedDRA coding dictionary used for the study at the time of database lock.

AEs will be presented for the following treatment groups: (1) double-blind active (Arm A in the DB Treatment Period), (2) double-blind placebo (Arm B in the DB Treatment Period), and (3) open-label active (OL Population Arm B). Treatment group comparisons refer to comparisons of events between double-blind active and double-blind placebo during the DB Treatment Period of the study. For the active treatment arm during the DB Treatment Period (Arm A), treatment emergent AEs are defined as any event that begins or worsens in severity after initiation of active study drug through 30 days after the last dose of active study drug. For the placebo arm (Arm B), treatment-emergent AEs during the DB Treatment Period are defined as any event that begins or worsens in severity after initiation of placebo through 30 days after the last dose of placebo and prior to OL Day 1 (if applicable). For subjects in the OL Population, treatment-emergent AEs are defined as any event that begins or worsens in severity after initiation of open-label study drug through 30 days after the last dose of open-label study drug.

The number and percentage of subjects in each treatment group with treatment-emergent AEs will be tabulated by primary MedDRA SOC and preferred term; comparisons between arms will be made using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent AEs by severity grade and relationship to study drug DAAs also will be provided. Subjects reporting more than one AE for a given MedDRA preferred term will be counted only once for that term using the event with the most severe grade for the severity grade tables and the most related event for the relationship to study drug tables. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

8.1.5.2 Clinical Laboratory Data

Clinical laboratory test values will be summarized by treatment group at each visit during the DB Treatment Period and separately for subjects treated in the OL Treatment Period. The baseline value will be the last measurement on or before the day of the first dose of double-blind study drug. This same baseline value will be used for all summary tables in the DB, OL, and Post-Treatment Periods.

Change from baseline to each post-baseline visit, including Final DB and OL Treatment Visits and applicable post-treatment visits, will be summarized for each protocol-specified laboratory parameter by treatment group; the baseline and visit means will be calculated along with the mean, standard deviation, and median for the change from baseline. 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. Separate tables will be used to summarize the changes from baseline to the DB Treatment Period visits (Arms A and B), the OL Treatment Period visits (Arm B), and the Post-Treatment Period visits (Arms A and B).

During the DB and OL Treatment periods, laboratory test values will be categorized as low, normal, or high based on reference ranges of the laboratory used in this study. Shift tables from baseline to minimum value and from baseline to maximum value during the DB and OL Treatment periods will be created. The shift tables will cross-tabulate, by treatment arm, the frequency of subjects with baseline values below/within/above the normal range versus minimum/maximum values below/within/above the normal range.

In addition, the number and percentage of subjects with post-baseline values during the DB and OL Treatment periods meeting pre-specified criteria for potentially clinically significant laboratory values or toxicity grades will be presented by treatment arm. Comparisons between arms will be performed on the percentage of subjects with laboratory abnormalities (by potentially clinically significant criterion or toxicity grade) during the DB Treatment Period for each parameter using Fisher's exact tests.

8.1.5.3 HIV-1 RNA Data

For the HCV/HIV co-infected subjects who were on stable HIV-1 ART at initiation of double-blind 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.

8.1.5.4 Vital Signs Data

Vital signs will be summarized by treatment group (DB active and DB placebo) at each visit during the DB Treatment Period and separately for subjects treated in the OL Treatment Period. The baseline value will be the last measurement on or before the day of the first dose of double-blind study drug. This same baseline value will be used for all summary tables in the DB, OL, and Post-Treatment Periods.

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each post-baseline visit, including Final DB and OL Treatment Visits, will be summarized descriptively by arm. The differences between the active and placebo arms in the DB Treatment Period will be analyzed using contrasts within an ANOVA model with treatment arm as the factor. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for potentially clinically significant vital sign values will be summarized by treatment arm, separately for the DB and OL Treatment Periods. Comparisons between arms will be performed on the percentage of subjects experiencing a value meeting the criteria during the DB Treatment Period for each parameter using Fisher's exact tests.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of ABT-530 and ABT-493 and possible metabolites and pharmacokinetic parameter values for ABT-493 and ABT-530 will be tabulated for each subject and group. Summary statistics will be computed for each time and visit.

Plasma concentration data from this study may be combined with data from other studies and analyzed using the following general methodology:

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version VII, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent volume of distribution (V/F) of the PK analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. The evaluation criteria described below will be used to examine the performance of different models.

- The objective function of the best model is significantly smaller than the alternative model(s).
- The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).
- Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using either stepwise forward selection method, or generalized additive method (GAM) or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the

significance (at $P < 0.005$, corresponding to an increase in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

In general, all continuous covariates will be entered in the model, initially in a linear fashion, with continuous covariates centered around the median value. Linear or non-linear relationships of primary pharmacokinetic parameters with various covariates may also be explored. For example:

TVCLi = Theta(1) + Theta(2) (Comedication [1,2,…]) + Theta(3) (WTi-median value) + Theta(4) (AGEi – median value).

Where TVCLi = Typical value of clearance for an individual, Theta(1) is the intercept and Theta(2) – (4) are regression parameters relating the fixed effects (weight and age centered on the median value) to clearance.

Relationship between exposure and clinical observations (antiviral activity) will be explored. Exposure-response relationships for primary and secondary efficacy variables and/or some safety measures of interest may also be explored.

The relationship between exposure (e.g., population pharmacokinetic model predicted concentrations over time or average concentrations or AUC or trough concentrations of the individual model-predicted pharmacokinetic profiles, or some other appropriate measure of exposure) and antiviral activity will be explored.

Logistic regression analyses will explore the relationship between exposure and one or more virologic endpoints (e.g., SVR_{12}, relapse following end of treatment and breakthrough on treatment).

Additionally, relationship between exposure and safety endpoints of interest may also be explored. Additional analyses will be performed if useful and appropriate.

8.2 Determination of 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. The expected approximate number of subjects by subpopulation is presented is Table 9.

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. To establish efficacy, the lower bound of a 2-sided 95% 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 Post Treatment 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. 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 Post Treatment 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. 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 Post Treatment Week 12 (after imputing) are counted as failures for SVR_{12}.

Table 9. 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 Country(ies)	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 Country(ies)	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 Country(ies)	96	48	144
HCV/HIV Co-infected	*8*	*4*	*12*
Not HCV/HIV Co-infected	*88*	*44*	*132*

8.2.1 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) to be 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% is being 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 3-DAA ± RBV in the Phase 3 trials among subjects dosed according to USPI and SmPC recommendations was 97% (870/894 patients),[21] 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).[20]

In the Global Phase 3 study of GT2-infected subjects without cirrhosis (Study M15-464), a historical control rate of 95% is being used with a non-inferiority margin of 6%, resulting in a threshold of 89%. This historical control rate is based on the regimen of SOF + RBV for 12 weeks of treatment (Table 10).

Table 10. 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[33]	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.[25]

The Global Phase 3 study of GT3-infected subjects without cirrhosis (Study M13-594) is 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.[26] 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 will be enrolled in Study M13-594. A 6% non-inferiority margin will be 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) is an open-label single-arm study. The analysis of the primary endpoint (SVR_{12}) is 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 11. 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 11. 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.

8.3 Randomization Methods

The randomization will be stratified by geographic region (China, Singapore, South Korea), genotype (GT1, GT2, combined GT3 – 6), and HCV/HIV co-infection status (co-infected, not co-infected). In China, eligible subjects will be randomized to Arm A or Arm B in the following ratios: 2:1 for GT1, 2:1 for GT2, and 2:1 for combined GT3 – 6. In Singapore and South Korea, eligible subjects will be randomized to Arm A or Arm B in the following ratios: 2:1 for GT1 and 2:1 for GT2.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or

advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Optional pharmacogenetic and optional intensive PK samples will only be collected if the subject has voluntarily signed and dated a separate informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate pharmacogenetic and intensive PK informed consents must be signed before the samples are collected and testing is performed. If the subject does not consent to either pharmacogenetic or intensive PK testing, it will not impact the subject's participation in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the

study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any optional pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, nor the subject, will be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional pharmacogenetic research may be used in scientific publications or presented at medical conventions. Optional pharmacogenetic research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for ABT-493 and ABT-530.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	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
Protocol Date:	03 April 2017

Signature of Principal Investigator Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Clinical
		Clinical
		Clinical
		CPPM
		Statistics
		Bioanalysis
		Clinical Drug Supply Management

Appendix C. Study Activities

Double-Blind Treatment Period

Activity	Screening	Day 1[a]	Week 1	Week 2	Week 4	Week 8*	Week 12[#]	Week 8 EOT/Week 16 EOT or Premature D/C from Treatment[b]
Informed Consent[c]	X							
Medical History[d]	X	X						
Physical Examination	X	X						X
Vital Signs, Weight, Waist Circumference,[e] Height[e]	X	X	X	X	X	X	X	X
12-lead ECG	X							X
Hematology/Chemistry/Urinalysis/Coagulation Panel, FSH[f]	X	X	X	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[g]	X (s)	X (u)			X (u)	X (u)	X (u)	X (u)
HBsAg, HBV DNA,[h] HCV Ab, HIV Ab Tests	X							
Drug/Alcohol Screen	X							
HbA1c[i]	X							
HCV Genotype and Sub-genotype	X							
FibroTest and APRI, FibroScan®[j] or Liver Biopsy[j]	X							
IL28B Sample[k]		X						
Optional Pharmacogenetic Sample[c,k]		X						
Total Insulin		X						

Activity	Screening	Day 1[a]	Week 1	Week 2	Week 4	Week 8*	Week 12#	Week 8 EOT/Week 16 EOT or Premature D/C from Treatment[b]
Concomitant Medication Assessment	X	X	X	X	X	X	X	X
Adverse Event Assessment[l]	X	X	X	X	X	X	X	X
Patient Reported Outcomes Instruments (PROs)[m]		X			X		X	X
Dispense Study Drug		X			X	X[n]	X[n]	X[o]
Study Drug Accountability[p] and Review of Study Drug Adherence			X	X	X[p]	X[p]	X[p]	X[p]
HCV RNA Sample	X	X	X	X	X	X	X	X
HIV-1 RNA[q,r]	X	X		X	X	X	X	X
HCV Resistance Sample		X	X	X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X	X	X
Flow Cytometry Sample[q]	X	X			X		X	X
Pharmacokinetic Samples for subjects who do not participate in the Optional Intensive PK sampling[s]			X	X	X	X	X	X
Pharmacokinetic Samples for subjects who do participate in the Optional Intensive PK sampling[c,s]		X[t]	X	X	X[t]	X	X	X

EOT = End of treatment; D/C = Discontinuation

* The EOT visit can be at Week 8 or Week 16 depending on treatment assigned.

\# Applicable only to those subjects enrolled into a 16-week treatment.

a. All procedures to be performed prior to first dose, with exception of the additional (optional) post-dose pharmacokinetic samples (Section 5.3.2.1).

b. Subjects who prematurely discontinue the Treatment Period should return to the site to complete the Premature Discontinuation Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).
c. Subjects need to sign an IRB/IEC approved informed consent for the study (prior to performing any screening or study-specific procedures) and the optional Pharmacogenetic Sample and Intensive PK sample(s), if applicable.
d. A complete medical history will be taken at Screening and will be updated at the Study Day 1 Visit.
e. Height will be measured at the Screening Visit only. Waist circumference will be measured at the Screening Visit, but if it is not measured at Screening, it may be measured on Day 1.
f. Only at Screening, for female subjects to assess postmenopausal state.
g. Pregnancy testing is not required for females of non-childbearing potential as defined in Inclusion Criterion 3.
h. Perform the test for HBV DNA if HBsAg is negative.
i. For those with history of diabetes mellitus.
j. For subjects who have not had a qualifying liver biopsy within the previous 24 months or a qualifying FibroScan® within the previous 6 months.
k. If the sample is not collected at Study Day 1, it may be collected at any other visit during the study.
l. See specific information regarding adverse event collection in Section 6.1.4.
m. PROs should be administered before any study procedures. EOT PROs are at Week 8 EOT or Week 16 EOT, as applicable.
n. Applicable only to those subjects enrolled into a 16-week treatment.
o. Open-Label study drug will be dispensed to those subjects randomized to Arm B in the DB Treatment Period.
p. Subjects should bring all the study drug to the study drug accountability visits at Weeks 4, 8, 12, EOT or Premature D/C. The site will record the number of tablets returned at these visits.
q. HCV/HIV co-infected subjects only.
r. For HCV/HIV co-infected subjects on stable ART: As detailed in Section 5.4.1.2, a repeat HIV-1 RNA blood draw to confirm a HIV-1 RNA result of ≥ 200 copies/mL can be done as an unscheduled visit, but must be performed at least 2 weeks apart from the prior HIV-1 RNA result. At the time the repeat plasma HIV-1 RNA is drawn, a sample may be obtained for HIV-1 resistance testing. If the confirmatory HIV-1 RNA lab draw falls on the date of a scheduled study visit, only a single HIV-1 RNA and HIV-1 resistance blood draw is needed at the visit.
s. Details regarding timing of PK samples are provided in Section 5.3.2.1.
t. For subjects participating in Optional Intensive PK sampling, additional PK samples will be drawn on Study Day 1 at 2, 4 and 6 hours post-dose and on Week 4 visit immediately prior to dose (0 hour) and 2 and 4 hours post-dose during the visit.

Open-Label Treatment Period

Activity	Day 1	Week 1	Week 2	Week 4	Week 8*	Week 12[#]	Week 8 EOT/Week 16 EOT or Premature D/C from Treatment[a]
First Dose of Active Drug	X[b]						
Physical Examination							X
Vital Signs, Weight		X	X	X	X	X	X
12-lead ECG							X
Hematology/Chemistry/Urinalysis/Coagulation Panel		X	X	X	X	X	X
Pregnancy Test (urine [u])[c]				X (u)	X (u)	X (u)	X (u)
Concomitant Medication Assessment		X	X	X	X	X	X
Adverse Event Assessment[d]		X	X	X	X	X	X
Dispense Study Drug				X	X[e]	X	
Study Drug Accountability[f] and Review of Study Drug Adherence		X	X	X[f]	X[f]	X[f]	X[f]
HCV RNA Sample		X	X	X	X	X	X
HIV-1 RNA[g,h]		X	X	X	X	X	X
HCV Resistance Sample		X	X	X	X	X	X
Archive Plasma Sample		X	X	X	X	X	X
Flow Cytometry Sample[g]				X		X	X
Pharmacokinetic Samples for subjects who do not participate in the Optional Intensive PK sampling[i]		X	X	X	X	X	X
Pharmacokinetic Samples for subjects who do participate in the Optional Intensive PK sampling[i]		X	X	X[j]	X	X	X

EOT = End of treatment; D/C = Discontinuation

* The EOT visit can be at Week 8 or Week 16 depending on treatment assigned.

Applicable only to those subjects enrolled into a 16-week treatment.

a. Subjects who prematurely discontinue the OL Treatment Period should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).

b. Subjects will take the first dose of Open-Label study drugs the day after the last day of the DB Treatment Period. The site will call the subject and record the study drug start date in the EDC system and source documents. The study drug end date of drug will be recorded in EDC and the source at OL Week 8 EOT/Week 16 EOT or Premature D/C from treatment.

c. Pregnancy testing is not required for females of non-childbearing potential as defined in Inclusion Criterion 3.

d. See specific information regarding adverse event collection in Section 6.1.4.

e. Applicable only to those subjects enrolled into a 16-week treatment.

f. Subjects should bring all the study drug to the study drug accountability visits at Weeks 4, 8, 12, EOT or Premature D/C. The site will record the number of tablets returned at these visits.

g. HCV/HIV co-infected subjects only.

h. For HCV/HIV co-infected subjects on stable ART: As detailed in Section 5.4.1.2, a repeat HIV-1 RNA blood draw to confirm a HIV-1 RNA result of ≥ 200 copies/mL can be done as an unscheduled visit, but must be performed at least 2 weeks apart from the prior HIV-1 RNA result. At the time the repeat plasma HIV-1 RNA is drawn, a sample may be obtained for HIV-1 resistance testing. If the confirmatory HIV-1 RNA lab draw falls on the date of a scheduled study visit, only a single HIV-1 RNA and HIV-1 resistance blood draw is needed at the visit.

i. Details regarding timing of PK samples are provided in Section 5.3.2.1.

j. For subjects participating in Optional Intensive PK sampling, additional PK samples will be drawn on the Week 4 visit immediately prior to dose (0 hour) and 2 and 4 hours post-dose during the visit.

Post Treatment Period

Activity	PT Week 4	PT Week 12	PT Week 24 or PT D/C[a]
Vital Signs and Weight	X	X	X
Hematology/Chemistry/Urinalysis/Coagulation Panel	X		X[b]
Pregnancy Test (urine)[c]	X (u)		X (u)[b]
Concomitant Medication Assessment[d]	X	X	X
PRO Instruments[e]		X	X
Adverse Event Assessment[f,g]	X	X	X
HCV RNA Sample	X	X	X
HIV-1 RNA[h,i]	X	X	X
HCV Resistance Sample	X	X	X
Flow Cytometry Sample[h]	X	X	X
Archive Plasma Sample	X	X	X

PT = Post Treatment

a. Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT Discontinuation Visit procedures.

b. Hematology/Chemistry/Urinalysis/Coagulation Panel and Pregnancy Test are not required at PT Week 24, but only at PT D/C if subject discontinued prior to PT Week 4.

c. Urine Pregnancy testing is not required in the PT Period for women that are not of childbearing potential.

d. Only medications taken for SAEs and treatment of HCV and HIV will be collected after 30 days post-dosing.

e. PROs should be administered before any study procedures. PROs at PT WK 12 and PT WK 24 only required for subjects randomized to Arm A.

f. All AEs (whether solicited or spontaneously reported by the subject) will be collected until 30 days post dosing.

g. After 30 days following completion of study treatment, and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected) (Section 6.1.4).

h. HCV/HIV co-infected subjects only.

i. For HCV/HIV co-infected subjects on stable ART: As detailed in Section 5.4.1.2, a repeat HIV-1 RNA blood draw to confirm a HIV-a RNA result of ≥ 200 copies/mL can be done as an unscheduled visit, but must be performed at least 2 weeks apart from the prior HIV-1 RNA result. At the time the repeat plasma HIV-1 RNA is drawn, a sample should be obtained for HIV-1 resistance testing. If the confirmatory HIV-1 RNA lab draw falls on the date of a scheduled study visit, only a single HIV-1 RNA and HIV-1 resistance blood draw is needed at the visit.

Note: Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.

Appendix D. List of AIDS-Associated Opportunistic Infections

Collection of data regarding known AIDS-associated opportunistic infections is covered in Section 6.1.8.

- Aspergillosis
- Bartonellosis
- Candidiasis (*Bronchi; *Esophagus; *Lungs; Oropharyngeal [Thrush]; *Trachea; Vulvovaginal [Persistent, Frequent, or Poorly Responsive to Therapy])
- *Coccidioidomycosis
- *Cryptococcosis
- *Cryptosporidiosis
- Cytomegalovirus (*Retinitis; *Cytomegalovirus Disease [other than liver, spleen or nodes])
- Enteric infections, Recurrent (Bacterial)
- Herpes Simplex Virus (*Bronchitis; *Esophagitis; *Pneumonitis; *Chronic Ulcer(s) [> 1 month in duration])
- *Histoplasmosis
- Human Herpesvirus-8 Disease (Kaposi Sarcoma, Primary Effusion Lymphoma, Multicentric Castleman's Disease)
- Human Papilloma Virus Infections
- *Isosporiasis (Cystoisosporiasis)
- Microsporidiosis
- *Mycobacterium avium – Complex Disease (Disseminated)
- *Mycobacterium tuberculosis – Infection and Disease
- *Pneumonia
- *Pneumonia, recurrent bacterial (and/or other respiratory infections including sinusitis, bronchitis, otitis)
- *Progressive multifocal leukoencephalopathy (JC Virus Infection)
- Syphilis

- *Toxoplasma Gondii Encephalitis
- Varicella Zoster Virus Diseases

* AIDS-defining event as described by CDC Surveillance Case Definition of 1993.[34]

Document Approval

Study M15592 - 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 - Original - 03Apr2017

Version: 3.0 **Date:** 05-Apr-2017 02:30:20 PM **Company ID:** 04052017-00F9F681054401-00003-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	03-Apr-2017 05:05:32 PM	Approver
	03-Apr-2017 05:28:53 PM	Author
	03-Apr-2017 06:33:17 PM	Accepter
	03-Apr-2017 08:43:55 P	Approver
	04-Apr-2017 01:10:27 AM	Approver
	04-Apr-2017 03:51:25 PM	Approver
	04-Apr-2017 09:13:06 P	Approver
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