1.0 Title Page

Clinical Study Protocol M15-828

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

Including Administrative Change 1 and Amendments 1 and 2

AbbVie Investigational Product:	ABT-493/ABT-530
Date:	17 June 2016
Development Phase:	3
Study Design:	This is a randomized, open-label, active comparator, multicenter study.
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie GK*
Sponsor/Emergency Contact:	Urgent contact during business hours: [redacted] Urgent contact after business hours (at night or on holidays): [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 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	18 December 2015
Administrative Change 1	19 May 2016
Amendment 1	29 January 2016

The purpose of this amendment is to:

- Update to how subjects will be randomized.

  Rationale: *To provide clarification on the stratification/randomization of subjects using Screening HCV RNA values.*
- Update to Section 5.2.3.1, Prior HCV Therapy.

  Rationale: *To provide additional guidance how subjects will be categorized.*
- Update to Section 5.3.5, Safety Variables.

  Rationale: *To provide clarification on safety variables.*
- Correct inconsistencies and typographical errors throughout the protocol.

An itemized list of all changes made to this protocol under this amendment can be found in Appendix D.

1.2 Synopsis

AbbVie GK	**Protocol Number:** M15-828
Name of Study Drug: ABT-493/ABT-530	**Phase of Development:** 3
Name of Active Ingredient: ABT-493, ABT-530	**Date of Protocol Synopsis:** 17 June 2016
Protocol Title: A Randomized, Open-Label, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults with Genotype 2 Chronic Hepatitis C Virus Infection (CERTAIN-2)	
Objective: The primary objectives of this study are to assess the efficacy (sustained virologic response 12 weeks post treatment, SVR_{12}) and safety of 8 weeks of treatment with the combination regimen ABT-493/ABT-530 in comparison to sofosbuvir (SOF) plus ribavirin (RBV) for 12 weeks in HCV GT2-infected subjects.	
Investigators: Multicenter, investigator information on file at AbbVie	
Study Sites: Approximately 60 sites.	
Study Population: DAA treatment-naïve, HCV GT2-infected non-cirrhotic Japanese adults, at least 18 years of age at time of Screening.	
Number of Subjects to be Enrolled: Approximately 120 subjects.	
Methodology: This is a Phase 3, randomized, open-label, active-control, multicenter study to evaluate the efficacy, safety and pharmacokinetics of ABT-493/ABT-530 for 8-weeks compared to the treatment regimen currently approved in Japan of sofosbuvir plus ribavirin for 12 weeks in chronic HCV GT2-infected DAA treatment-naïve subjects without cirrhosis. The study will consist of: <u>Treatment Period</u> HCV GT2-infected DAA treatment-naïve subjects (including subjects who are interferon [IFN] treatment experienced with or without RBV) without cirrhosis will be randomized in a 2:1 ratio to one of the two treatment arms: • Arm A: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks (80 subjects) • Arm B: SOF 400 mg QD plus RBV (600 – 1000 mg based on weight divided BID) for 12 weeks (40 subjects) The randomization will be stratified by prior IFN-experience (naïve versus experienced) and Screening HCV RNA (< or ≥ 6 million IU/mL). Scheduled visits for subjects in the Treatment Period who are assigned to the 8-week regimen of ABT-493/ABT-530 consist of Day 1 and Weeks 1, 2, 4 and 8. For subjects assigned to the 12-week regimen of SOF plus RBV, scheduled visits in the Treatment Period consist of Day 1 and Weeks 1, 2, 4, 8 and 12. Study procedures, including assessment of adverse events, vital signs, treatment adherence, concomitant medications, HCV RNA, pharmacokinetic assays for ABT-493, ABT-530 and active comparators, and clinical laboratory tests, will be conducted at each visit.	

Methodology (Continued):

Post-Treatment Period

Subjects who complete the Treatment Period, experience on treatment virologic failure, or prematurely discontinue study drug will be followed for 24 weeks to monitor safety, HCV RNA levels, and to evaluate efficacy and the emergence and persistence of viral resistance-associated variants.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Japanese male or female subjects at least 18 years of age at time of screening.
2. Female who is:
   - not of childbearing potential, defined as:
     - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state), or
     - surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s);
   - of childbearing potential and sexually active with male partner(s):
     - currently using at least one effective method of birth control at the time of screening and agrees to practice one effective method of birth control for subjects randomized to Arm A and two effective methods of birth control for subjects randomized to Arm B while receiving study drugs (non-hormonal intrauterine device [IUD], subject or partner[s] using condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams), starting with Screening and for 30 days after stopping study drug for Arm A subjects and 6 months after stopping study drug for Arm B subjects. (Note that both contraceptive sponge and vaginal ring with spermicidal jellies or creams are unapproved in Japan.)
3. Sexually active males must be surgically sterile, or if sexually active with female partner(s) of childbearing potential must agree to practice one effective form of birth control (partner[s] using IUD [including those containing hormonal contraceptives], subject or partner[s] using condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams), starting with Screening and through 30 days after stopping study drug for Arm A subjects and 6 months after stopping study drug for Arm B subjects. (Note that both contraceptive sponge and vaginal ring with spermicidal jellies or creams are unapproved in Japan.)
4. Screening central laboratory result indicating HCV GT2 infection without co-infection of any other genotype.
5. Subject has positive anti-HCV Ab and plasma HCV RNA viral load $\geq$ 1000 IU/mL at Screening Visit.
6. Chronic HCV infection defined as one of the following:
   - Positive for anti-HCV antibody (Ab) and/or HCV RNA at least 6 months before Screening.
   - A liver biopsy consistent with chronic HCV infection.

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

Main Inclusion (Continued):

7. Subject must be HCV DAA treatment-naïve (i.e., patient has not received a single dose of any approved or investigational DAA). Prior HCV treatment using IFNs with or without ribavirin is acceptable. Previous HCV IFN based treatment must have been completed ≥ 2 months prior to screening.
8. 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.
9. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
10. 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, New Inuyama or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4;
    - A FibroScan® score of < 12.5 kPa within 6 months of Screening or during the Screening Period;
        - Subjects with indeterminate FibroScan® score (12.5 ≤ score < 14.6), must have a qualifying liver biopsy.
    - A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2;
        - Subjects with indeterminate FibroTest, or conflicting FibroTest and APRI results (e.g., FibroTest ≤ 0.72, but APRI > 2 or FibroTest ≥ 0.73, but APRI ≤ 2) must have a qualifying FibroScan® or liver biopsy.
    - A screening Discriminant Score (z) less than zero, according to the following formula: $z = 0.124 \times [\text{gamma-globulin (\%)}] + 0.001 \times [\text{hyaluronate } (\mu g \times l^{-1})] - 0.075 \times [\text{platelet } (\times 10^4 \text{ cells/mm}^3)] - 0.413 \times \text{gender (male, 1; female, 2)} - 2.005$.
        - Subjects with indeterminate Discriminant Score (score = 0), must have a qualifying FibroScan® or liver biopsy.

Main Exclusion:

1. Female who is pregnant, planning to become pregnant during the study, or breastfeeding; or male whose partner is pregnant or planning to become pregnant during the study.
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 anti human immunodeficiency virus antibody (HIV Ab).
4. 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.

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

Main Exclusion (Continued):

5. Clinically significant abnormalities, other than HCV-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, or any history of HCC.
   - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection.
6. 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, or steatohepatitis considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection.
7. History of solid organ transplantation.
8. 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.
9. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-493/ABT-530.
10. History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.
11. Patients who can't participate in study per local law.
12. Any current or past clinical evidence of decompensated liver disease such as ascites noted on physical exam, hepatic encephalopathy or esophageal variceal bleeding.
13. Screening laboratory analyses showing any of the following abnormal laboratory results:
    - Creatine Clearance (CrCl) $\leq$ 50 mL/min
    - Albumin: < LLN
    - International normalized ratio (INR): $\geq$ 1.2 (Subjects with a known inherited blood disorder and INR $\geq$ 1.2 may be enrolled with permission of the AbbVie TA MD.)
    - Hemoglobin: < 12 g/dL
    - Platelets: < 90,000 cells per mm^3

Investigational Products:	ABT-493/ABT-530 100 mg/40 mg tablet
Doses:	ABT-493/ABT-530 300 mg/120 mg QD (3 × 100 mg/40 mg tablets)
Mode of Administration:	Oral after food
Reference Therapy:	sofosbuvir (SOF) 400 mg tablet plus ribavirin (RBV) 200 mg capsule
Doses:	SOF 400 mg QD plus RBV 600 – 1000 mg based on weight divided BID
Mode of Administration:	Oral

Duration of Treatment: Subjects will receive ABT-493/ABT-530 for 8 weeks. Subjects will receive SOF plus RBV for 12 weeks.

Criteria for Evaluation:

Efficacy:

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

Resistance:

The following information will be tabulated and summarized: 1) for all subjects receiving ABT-493/ABT-530 with available samples, the variants at baseline at signature resistance-associated amino acid positions relative to the appropriate prototypic reference sequence; and 2) for subjects receiving any study drugs who do not achieve SVR_{12}, post-baseline variants relative to baseline.

Pharmacokinetic:

Individual plasma concentrations of ABT-493, ABT-530, SOF, GS-331007, RBV and their possible metabolites will be tabulated and summarized. Values for pharmacokinetic parameters of ABT-493, ABT-530, SOF, GS-331007, RBV and their possible metabolites including apparent clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using population pharmacokinetic modeling procedures.

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.

Safety:

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

Statistical Methods:

Efficacy:

The ITT population will include all randomized subjects who receive at least one dose of study drug. The primary efficacy variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

The primary efficacy endpoint is:

- Non-inferiority of ABT-493/ABT-530 for 8-weeks (Arm A) to SOF/RBV for 12 weeks (Arm B) in SVR_{12} using a non-inferiority margin of 10%.

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

Statistical Methods (Continued):

Efficacy (Continued):

The following secondary endpoints will be summarized:

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

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

For the analysis of relapse, completion of treatment is defined as any subject assigned to the 12-week treatment (Arm B) with study drug duration of 77 days or greater; or any subject assigned to the 8-week treatment (Arm A) with study drug duration of 52 days or greater.

The percentage of subjects with on-treatment virologic failure, or post-treatment relapse will be summarized for each treatment arm. Two-sided 95% confidence intervals will be provided for the percentages within treatment arms and for the difference between arms (Arm A minus Arm B). Wilson score intervals will be used for within arm summaries and for any between arm summaries, unless otherwise specified.

Resistance:

For all subjects receiving ABT-493/ABT-530 and with available samples, the variants at signature resistance-associated amino acid positions at baseline identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence will be tabulated and summarized.

The following resistance information will be analyzed for subjects receiving any study drugs who do not achieve SVR_{12} and who have an available post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid variants in available post-baseline samples identified by population or deep sequencing in comparison to the baseline sequence, 2) the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population or deep sequencing in comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral variants by population or deep sequencing for subjects in Arm A.

Pharmacokinetic:

Plasma concentration of ABT-493, ABT-530, SOF, GS-331007, RBV and their possible metabolites will be tabulated for each subject and group. Summary statistics will be computed for each time and visit. 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.

Statistical Methods (Continued):

Patient Reported Outcomes (PROs):

The mean change from baseline to Final Treatment Visit and from baseline to Post-Treatment Week 12 in the FSS total score, EQ-5D-3L health index score and VAS score 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.

Safety:

All subjects who receive at least one dose of study drugs will be included in the safety analyses. 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 study arms, 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 are potentially clinically significant, according to predefined criteria, will be summarized.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APRI	Aminotransferase/platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area Under the Concentration Curve
BMI	Body Mass Index
BUN	Blood urea nitrogen
CRF	Case report form
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DNA	Deoxyribonucleic acid
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
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
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
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NONMEM	Non-linear mixed-effect modeling
NS5A	Nonstructural viral protein 5A
PI	Protease Inhibitor
PK	Pharmacokinetic
POR	Proof of Receipt
PRO	Patient Reported Outcome
PR	pegIFN/RBV
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
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class/Standard of Care
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

ULN	Upper limit of normal
VAS	Visual Analog Scale
V/F	Apparent Volume of distribution
WBC	White blood cells

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the plasma concentration-time curve
CL/F	Apparent oral plasma clearance
C_{max}	Maximum observed plasma concentration

Definition of Terms

Study Drug	ABT-493, ABT-530, SOF, RBV
Study Day 1	First day of study drug dosing
Treatment Period	Day 1 through last dose of study drug
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 170 million individuals infected worldwide.[1] There are 7 identified HCV genotypes,[2] with genotype 1 (GT1) being most prevalent worldwide. Depending on various risk factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis.[3] 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.[3] Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[3] 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.[4,5]

In Japan, it is estimated that 1.5 million individuals are HCV antibody positive and approximately 1 million of these are viremic. An estimated 70% of HCV patients in Japan are infected with HCV genotype 1 (mainly 1b), approximately 30% with genotype 2 and approximately 2% with other genotypes (3, 4, 5, or 6).[6-10] Due to an aging Japanese patient population and the associated disease progression, the health burden of chronic HCV infection in Japan is predicted to increase over the next several years.

The currently available HCV interferon-free treatment regimen in Japan for GT2 is sofosbuvir + RBV,[11] which was approved in March 2015. Evaluation of the 12-week SOF plus RBV regimen across multiple clinical trials (Table 1) resulted in an estimated SVR rate of 95% in GT2-infected non-cirrhotic subjects.

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

Trial	SVR (n/N)	SVR (%)
FISSION[14]	59/61	97%
POSITRON[14]	85/92	92%
FUSION[14]	26/29	90%
VALENCE[14]	59/63	94%
Japanese Study[11]	132/136	97%
Total	**361/381**	**95%**

There are currently no IFN-free regimens indicated for genotypes other than 1 and 2 in Japan, and no regimens that are indicated in both GT1 and GT2. The available IFN-free regimen for GT2 requires coadministration with RBV and is not indicated for those with renal impairment.[11] Despite recent treatment advances, unmet needs of HCV treatment in Japan remain and there is further opportunity to improve treatment options with pan-genotypic regimens that can treat all the HCV GTs in Japan with high SVR rates and highly tolerable regimens.

A next-generation 2-DAA regimen including ABT-493, an HCV NS3/4A protease inhibitor, and ABT-530, an NS5A inhibitor, are under development by AbbVie to further improve HCV treatment. These compounds are denoted as "next generation" because each has demonstrated potent antiviral activity against all major HCV GTs in vitro while maintaining potent antiviral activity against known common single-position resistant variants. Both compounds further demonstrated high barrier to resistance development in vitro.

ABT-493

ABT-493 is an NS-3/4A PI with potent and pangenotypic activity. It demonstrates a high genetic barrier to resistance with 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.[12]

ABT-530

ABT-530 is an NS5A inhibitor with pangenotypic activity and a high genetic barrier to resistance maintaining activity against all common single nucleotide change resistance associated variants in NS5A in all GTs. ABT-530 is > 100-fold more active than the first generation NS5A inhibitors (ombitasvir, daclatasvir, and ledipasvir) against key single-position resistance-associated variants.

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.[13]

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.

ABT-493 and ABT-530 combination has been well tolerated when administered to over 590 healthy volunteers (including Japanese and Han Chinese). Over 580 subjects have been dosed to-date with the combination of ABT-493 and ABT-530 in Phase 2 studies.

The combination of ABT-493 and ABT-530 has also been evaluated in Japanese and 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.

For a detailed discussion of drug-drug interaction and other Phase 1 studies please refer to the Investigator's Brochures for respective compounds.

Study M14-868 is an ongoing Phase 2b study assessing the efficacy, safety and pharmacokinetics of the combination of ABT-493 and ABT-530 in HCV GT2 and GT3-infected treatment-naïve (TN) and PR-experienced non-cirrhotic subjects. The study arms including the GT2 population, doses, duration, and preliminary SVR_4 and SVR_{12} results where available are presented in Table 2:

Table 2. SVR_4 and SVR_{12} in GT2 Subjects in Study M14-868

Study-Arm	Duration (Weeks)	493 Dose (mg QD)	530 Dose (mg QD)	RBV	N	SVR_4 n/N (ITT%)	SVR_{12} n/N (ITT%)	Virologic Failure*	Other
Non-cirrhotic GT2 (PegRBV exp or naïve)									
Part 1:									
M14-868-A	12	300	120	no	24	24/25 (96%)	24/25 (96%)	0	1 lost to follow-up
M14-868-B	12	200	120	no	24	24/24 (100%)	24/24 (100%)	0	
M14-868-C	12	200	120	yes	25	25/25 (100%)	25/25 (100%)	0	
Part 2:									
M14-868-J	8	300	120	no	54	53/54 (98%)	na**	0	1 lost to follow-up

* Virologic failure, includes failure to suppress, breakthrough on treatment or post-treatment relapse.

** Few subjects have reached Post Treatment Week 12.

High rates of SVR_4 and SVR_{12} and no virologic failures were observed across all GT2 non-cirrhotics in Study M14-868. The preliminary efficacy data for 8 weeks of treatment was similar to 12 weeks in GT2 non-cirrhotics, including treatment-naïve or pegIFN + RBV experienced subjects. Coadministration of ribavirin (Arm C) was not needed to improve efficacy.

Preliminary assessment of safety was performed in Part 1 of Studies M14-867 and M14-868. Study M14-867 is an ongoing Phase 2b study evaluating the efficacy, safety and pharmacokinetics of ABT-493 and ABT-530 in HCV GT1- through GT6-infected treatment naïve (TN) and PR-experienced non-cirrhotic subjects, and GT1-infected subjects with compensated cirrhosis. Safety data from 274 subjects in Studies M14-867 and M14-868 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) show that the most frequently reported adverse events were fatigue, nausea, and headache (occurring in > 5% and < 15% 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 in Part 1 of Studies M14-867 and M14-868, 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 in Arm F (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.

All subjects with baseline ALT elevations showed a trend toward ALT normalization or ALT became normal with DAA treatment, and there have been no on-treatment ALT elevations above baseline. Other laboratory abnormalities were infrequent and were primarily associated with well-described hemolytic effect of RBV, manifesting as Grade 1 anemia in a total of 4 subjects in the RBV-containing arms. Occasional Grade 1 or 2 total bilirubin elevations that were predominantly indirect, were mostly isolated occurrences, and normalized or stabilized with continued DAA therapy. The majority of these bilirubin elevations were observed in the RBV-containing arms.

Study M15-828 is a multi-center, randomized, active comparator, open label Phase 3 study intended to evaluate the safety and efficacy of 8 weeks of treatment with the combination regimen of ABT-493 and ABT-530 compared to the currently approved 12-week regimen of SOF plus RBV in DAA-naïve HCV GT2-infected patients without cirrhosis. For more information on the pharmacokinetics, drug-drug interactions, clinical efficacy and safety of the active comparator regimen, please refer to the package inserts for sofosbuvir[11,14] and ribavirin.[15]

Additional discussion and justification of study design may be found in Section 5.6.

3.1 Differences Statement

The current study (Study M15-828) is a Phase 3 study evaluating the efficacy, safety and pharmacokinetics of the ABT-493/ABT-530 combination regimen in the Japanese

population with chronic HCV GT2 infection. An on-going global Phase 2b study (Study M14-868) is assessing the efficacy, safety and pharmacokinetics of the combination regimen of ABT-493 and ABT-530 in HCV GT2-infected subjects without cirrhosis for treatment durations of 12 weeks (Part 1) and 8 weeks (Part 2).

In healthy volunteer studies (Studies M14-066 and M15-432) the pharmacokinetics of ABT-493 and ABT-530 were found to be similar between Caucasians and Japanese subjects. This, combined with preliminary efficacy and safety of 8 weeks of ABT-493 and ABT-530 in Study M14-868, provides supporting data and rationale for the advancement of the ABT-493 and ABT-530 combination regimen into this Phase 3 study, the first study of the regimen in HCV GT2-infected Japanese subjects. Study M15-828 will evaluate the selected dose and regimen of ABT-493/ABT-530 for 8 weeks using the co-formulated, fixed dose combination tablet intended for marketing and will include a Japanese subject population with chronic HCV GT2-infection which is DAA treatment-naïve, without cirrhosis.

3.2 Benefits and Risks

Preliminary efficacy data in Study M14-868 (Part 1) have demonstrated high efficacy with no virologic failure for ABT-493 300 mg QD in combination with ABT-530 120 mg QD in GT2-infected patients without cirrhosis treated for 8 and 12 weeks; Post-Treatment Week 4 results to date show that 98% (53/54) of subjects treated for 8 weeks achieved SVR_4 and 96% (24/25) of the subjects treated for 12 weeks achieved SVR_{12}.
Two subjects lost to follow-up and were considered non-responders.

In terms of safety, preliminary data across all arms in Study M14-868 (Part 1) using a regimen containing ABT-493 at a 300 mg dose (n = 55) demonstrate, no differences in the safety profile (including adverse events and LFT abnormalities) compared to arms using 200 mg ABT-493. No subjects in the study have experienced treatment-emergent ALT elevations.

Adverse events that are known, and those not previously described, may occur with the combination of the two DAAs, as detailed in the informed consent for 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-530 and ABT-493 co-administered including the risks of toxicity, virologic failure, and development of resistant mutations (Section 5.6.4), appear to be limited and manageable based upon the available data. Given the potential high SVR rate in these populations of HCV-infected subjects, the risk-benefit ratio is favorable.

An approved regimen, sofosbuvir plus ribavirin, will be used in the study as an active comparator and has been shown to be safe and efficacious (Table 2) in subjects with HCV GT2 infection.

4.0 Study Objective

4.1 Primary Objective

The primary objectives of this study are to assess the efficacy (SVR_{12}) and safety of 8 weeks of treatment with the ABT-493/ABT-530 combination regimen in comparison to SOF plus RBV for 12 weeks in DAA treatment-naïve, non-cirrhotic Japanese adults with chronic HCV GT2-infection.

4.2 Secondary Objective

The secondary objectives are to assess:

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

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

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

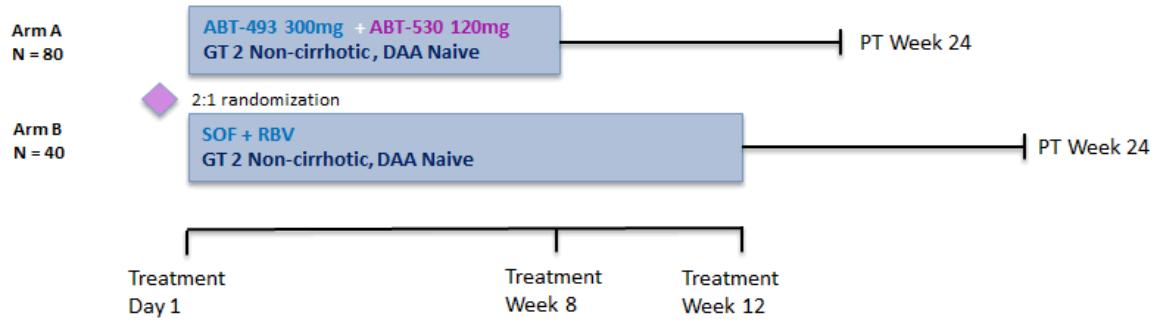
This is a Phase 3, randomized, open-label, active-control, multicenter study to evaluate efficacy, safety and pharmacokinetics of ABT-493/ABT-530 in chronic HCV GT2-infected DAA treatment-naïve Japanese adult subjects without cirrhosis. Subjects (including IFN treatment experienced with or without RBV) will be randomized in a 2:1 ratio to ABT-493/ABT-530 for 8 weeks (Arm A) or SOF plus RBV for 12 weeks (Arm B).

This study will consist of:

Treatment Period: Subjects will receive 8 weeks of ABT-493/ABT-530 or 12 weeks of SOF plus RBV.

Post-Treatment Period: Subjects who complete the Treatment Period, experience-on treatment virologic failure, or otherwise prematurely discontinue the Treatment Period will be followed for 24 weeks to monitor safety, HCV RNA levels, and to evaluate efficacy and the emergence and persistence of viral resistance-associate variants.

Figure 1. Study Schematic



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

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

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

The study was designed to enroll 120 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with 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.

The primary analysis will occur after all subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinue from the study.

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 may be retested or rescreened only once.

Subjects who have exclusionary laboratory parameter(s) per Exclusionary Criteria 13, Section 5.2.2, 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 or retested again.

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 upon retest/rescreen, the site personnel must contact the IRT and identify the subject as a screen failure.

5.1.2 Treatment Period

After meeting the eligibility criteria, subjects will be enrolled via IRT into 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 Treatment Period are detailed in Table 4. Safety and tolerability will be assessed throughout the study. Laboratory testing will include chemistry, hematology, and urinalysis as specified in Table 6. 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. Blood samples for optional pharmacogenetic analysis will be collected as detailed in Table 4.

All subjects will continue to return to the site on an outpatient basis as outlined in Table 4. Sites should ensure that subjects adhere to all study visits. Should a subject have an extraordinary circumstance which would preclude them from adhering to their originally scheduled visit date, visits in the Treatment Period will have an allowable visit window of

± 3 days. It should be noted and reinforced to subjects that SOF is supplied with the exact amount of tablets (28) needed between the study drug dispensation visits in Table 4. 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.

Virologic stopping criteria will be evaluated and applied by the investigator as detailed in Section 5.4.1.1.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Table 4 and as described in Section 5.4.1.1.

5.1.3 Post-Treatment Period

All subjects who received at least one dose of study drug and either complete treatment or prematurely discontinue the study drug will be monitored in the Post-Treatment Period for safety, HCV RNA and the emergence and persistence of resistant viral variants for an additional 24 weeks following the last dose of study drug.

The Post-Treatment Period will begin the day following the last dose of study drug treatment. Study visits during the Post-Treatment Period are detailed in Table 5. Should a subject have an extraordinary circumstance which would preclude them from adhering to their originally scheduled visit date, visits in the Post-Treatment Period will have an allowable visit window of ± 3 days.

Subjects who prematurely discontinue the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit as outlined in Table 5.

5.2 Selection of Study Population

The study population consists of chronic HCV GT2-infected Japanese male and females adults, without cirrhosis, who are HCV DAA treatment-naïve. Subjects who meet all the

inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Japanese male or female subjects at least 18 years of age at time of screening.
2. Female who is:
   - not of childbearing potential, defined as:
     - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state), or
     - surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s);
   - of childbearing potential and sexually active with male partner(s):
     - currently using at least one effective method of birth control at the time of screening and agrees to practice one effective method of birth control for subjects randomized to Arm A and two effective methods of birth control for subjects randomized to Arm B while receiving study drugs (non-hormonal intrauterine device [IUD], subject or partner[s] using condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams), starting with Screening and for 30 days after stopping study drug for Arm A subjects and 6 months after stopping study drug for Arm B subjects. (Note that both contraceptive sponge and vaginal ring with spermicidal jellies or creams are unapproved in Japan.)
3. Sexually active males must be surgically sterile, or if sexually active with female partner(s) of childbearing potential must agree to practice one effective form of birth control (partner[s] using IUD [including those containing hormonal contraceptives], subject or partner[s] using condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams), starting with Screening and through 30 days after stopping study drug for Arm A subjects and 6 months after stopping study drug for Arm B subjects. (Note that both

contraceptive sponge and vaginal ring with spermicidal jellies or creams are unapproved in Japan.)

4. Screening central laboratory result indicating HCV GT2-infection without co-infection of any other genotype.
5. Subject has positive anti-HCV 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 anti-HCV antibody (Ab) and/or HCV RNA at least 6 months before Screening; or
   - A liver biopsy consistent with chronic HCV infection.
7. Subject must be HCV DAA treatment-naïve (i.e., patient has not received a single dose of any approved or investigational DAA). Prior HCV treatment using IFNs with or without ribavirin is acceptable. Previous HCV IFN based treatment must have been completed ≥ 2 months prior to screening.
8. 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.
9. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
10. 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, New Inuyama or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4;
    - A FibroScan® score of < 12.5 kPa within 6 months of Screening or during the Screening Period;

- Subjects with indeterminate FibroScan® score (12.5 ≤ score < 14.6), must have a qualifying liver biopsy.

- A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2;
  - Subjects with indeterminate FibroTest, or conflicting FibroTest and APRI results (e.g., FibroTest ≤ 0.72, but APRI > 2 or FibroTest ≥ 0.73, but APRI ≤ 2) must have a qualifying FibroScan® or liver biopsy.
- A screening Discriminant Score (z) less than zero, according to the following formula: $z = 0.124 \times$ [gamma-globulin (%)] $+ 0.001 \times$ [hyaluronate ($\mu g \times l^{-1}$)] $-0.075 \times$ [platelet ($\times 10^4$ cells/mm^3)] $- 0.413 \times$ gender (male, 1; female, 2) $- 2.005$.
  - Subjects with indeterminate Discriminant Score (score = 0), must have a qualifying FibroScan® or liver biopsy.

Rationale for Inclusion Criteria

1, 4 – 7, 10	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, 9	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. Female who is pregnant, planning to become pregnant during the study, or breastfeeding; or male whose partner is pregnant or planning to become pregnant during the study.
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 anti human immunodeficiency virus antibody (HIV Ab).

4. 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.
5. Clinically significant abnormalities, other than HCV-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, or any history of HCC.
    - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection.
6. 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, or steatohepatitis considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection.
7. History of solid organ transplantation.
8. 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.
9. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-493/ABT-530.

10. History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.
11. Patients who can't participate in study per local law.
12. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history of decompensated liver disease such as ascites noted on physical exam, hepatic encephalopathy or variceal bleeding.
13. Screening laboratory analyses showing any of the following abnormal laboratory results:
    - Creatine Clearance (CrCL) ≤ 50 mL/min
    - Albumin: < LLN
    - International normalized ratio (INR): ≥ 1.2 (Subjects with a known inherited blood disorder and INR ≥ 1.2 may be enrolled with permission of the AbbVie TA MD.)
    - Hemoglobin: < 12 g/dL
    - Platelets: < 90,000 cells per mm^3

Rationale for Exclusion Criteria

1, 5, 7, 9 – 13	In order to ensure safety of the subjects throughout the study
2, 4, 8	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
3, 6	To exclude subjects with HIV or liver diseases other than chronic HCV GT2 infection

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, traditional medicines and/or herbal supplements) that the subject is receiving from the time of signing the consent through the Treatment Period 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.

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 assessed as related to the study drugs and treatment of HCV will be recorded thereafter.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior HCV Therapy

Subjects must be HCV DAA treatment-naïve (i.e., subject has never received a single dose of such agents). Prior treatment, such as interferons, with or without RBV, is acceptable. Previous HCV IFN based treatment must have been completed ≥ 2 months prior to the Screening Visit.

Subjects will be categorized as:

- Treatment-naïve: subject has never received any treatment for HCV infection.
- Subjects **with prior Interferon-based treatment** will be categorized as:
  - **Non-responder:** HCV RNA detected (or quantifiable) 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 (or unquantifiable) at the end of treatment;
    - Unknown or unable to specify: insufficient data to categorize as null or partial responder.

- **Breakthrough:** confirmed ≥ 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 (or unquantifiable) at the end of a prior treatment course but HCV RNA was detectable (or quantifiable) 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 IFN-based therapy at least 2 months prior to the Screening Visit in order to be eligible for the study.

5.2.3.2 Concomitant Therapy

Subjects should be on a stable dose of concomitant medications for at least 2 weeks prior to initiation of study drugs. The investigator should confirm that a concomitant medication/supplement can be safely administered with study drugs. Some medications may require dose adjustments due to the potential for drug-drug interactions.

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. While the subject is using hepatoprotective medication, the dose should be kept stable. When Investigators need to adjust hepatoprotective medications based on the Investigator's medical assessment, investigator must first consult with the AbbVie TA MD before making any adjustment of hepatoprotective medications.

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, 30 days following discontinuation of study drugs, if applicable.

5.2.3.3 Prohibited Therapy

Subjects must be able to safely discontinue any prohibited medications or supplements listed in Table 3 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 Treatment Period and for 30 days following discontinuation of study drugs.

Table 3. Prohibited Medications and Supplements

Medication or Supplement Name*
Any herbal medicines or supplements (excluding hepatoprotective agents), red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, pitavastatin, simvastatin**
Astemizole, cisapride, terfenadine, bosentan, oxcarbazepine, silodosin, efavirenz, atazanavir, ethinyl estradiol-containing contraceptives

* The use of SOF plus RBV is prohibited with the following drugs: rifampicin, carbamazepine, phenytoin, St. John's Wort-containing food; and should be administered with care with: rifabutin, phenobarbital, didanosine, and zathioprine.

** Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, pitavastatin, 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.

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).

Anti-HCV medications other than those specified in the protocol will not be allowed during the Treatment Period of the study.

The investigator must refer to the current SOF and RBV package inserts or product labels for a complete list of prohibited medications for subjects randomized to the SOF plus RBV treatment arm (Arm B).

5.3 Efficacy, Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Table 4 and Table 5.

Table 4. Treatment Period

Activity	Screening	Day 1[a]	Week 1	Week 2	Week 4	Week 8*	Wk 8 EOT*, Week 12 EOT*, or Premature Discontinuation 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
ECG	X						
Hematology/Chemistry/Urinalysis/Coagulation Panel	X	X	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[f]	X (s)	X (u)			X (u)	X (u)	X (u)
HBsAg, anti-HCV Ab, anti-HIV Ab Tests	X						
FSH (all females)	X						
Drug/Alcohol Screen	X						
HgbA1c[g]	X						
HCV Genotype and Sub-genotype	X						
Discriminant Score or FibroTest and APRI, or FibroScan®[h] or Liver Biopsy[h]	X						
IL28B Sample[i]		X					
Pharmacogenetic Sample (optional)[i]		X					
Total Insulin		X					X

Table 4. Treatment Period (Continued)

Activity	Screening	Day 1[a]	Week 1	Week 2	Week 4	Week 8*	Wk 8 EOT*, Week 12 EOT*, or Premature Discontinuation from Treatment[b]
Concomitant Medication Assessment	X	X	X	X	X	X	X
Adverse Event Assessment[j]	X	X	X	X	X	X	X
Patient Reported Outcomes Instruments (PROs)[k]		X					X
Study Drug Dispensed		X			X	X[o]	
Study Drug Accountability, Review Study Drug Diary and Review of Study Drug Adherence[l]		X	X	X	X	X	X
HCV RNA Samples	X	X	X	X	X	X	X
HCV Resistance Sample		X	X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X	X
Pharmacokinetic Samples[m]		X[n]	X	X	X[n]	X	X

EOT = End of treatment

* The EOT visit can be at Weeks 8 or 12 depending on treatment assignment.

a. All procedures to be performed prior to first dose, with the 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 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.

Table 4. Treatment Period (Continued)

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. Pregnancy testing is not required for females of non-childbearing potential as defined in Inclusion Criterion 2.

g. For those with history of diabetes mellitus.

h. For subjects who have not had a qualifying liver biopsy within the previous 24 months or a qualifying FibroScan® within the previous 6 months.

i. If the IL28B sample or the optional Pharmacogenetic sample is not collected at Study Day 1, it may be collected at any other visit during the study.

j. See specific information regarding adverse event collection in Section 6.1.1.1.

k. PROs should be administered before any study procedures. EOT PROs are at Weeks 8 or 12, as applicable.

l. Subjects should bring all study drugs to every visit for the site to review adherence. However, the site will record the number of tablets returned only at the Study Drug Accountability Visits at Weeks 4, 8 or Premature Discontinuation.

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

n. 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. Refer to specific details provided in Section 5.3.2.1.

o. For subjects enrolled into Arm B with 12 weeks of treatment.

Table 5. Post Treatment Period

Activity	PT Week 2	PT Week 4	PT Week 8	PT Week 12	PT Week 24 or PT Discontinuation[a]
Vital Signs and Weight	X	X	X	X	X
Hematology/Chemistry/Urinalysis/Coagulation Panel		X			X[b]
Pregnancy Test (urine)[c]		X (u)	X[d]	X[d]	X (u)[b,c,d]
Concomitant Medication Assessment[e]	X	X	X	X	X
PRO Instruments[f]				X	
Adverse Event Assessment[g]	X	X	X	X	X
HCV RNA Samples	X	X	X	X	X
HCV Resistance Sample	X	X	X	X	X
Archive Plasma Sample	X	X	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 only required at Post Treatment Discontinuation 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. For subjects in the RBV-inclusive regimen (Arm B), subjects must have a urine pregnancy test performed every month and may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site at PT Weeks 16 and 20. Additional testing may be required per local RBV label.

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

f. PROs should be administered before any study procedures.

g. Nonserious AEs and all SAEs will be collected until 30 days post dosing. Only SAEs will be collected thereafter (see Section 6.1.4).

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

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 illicit/illegal drug use, will be taken at Screening. The subject's medical history will be updated on Study Day 1 Visit. 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 Table 4, or upon subject discontinuation. A symptom-directed physical examination will be performed when necessary.

The physical examination performed on Study 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 not measured at Screening, it may be measured on Study Day 1.

Vital Signs and Weight

Body temperature, blood pressure, pulse and weight will be measured at each study visit as specified in Table 4 and Table 5 or upon subject discontinuation. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. The subject will wear lightweight clothing and no shoes during weighing.

12-Lead Electrocardiogram (ECG)

A 12-lead resting ECG will be obtained at the visit indicated in Table 4. The ECG should be performed prior to blood collection.

The ECG will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign, and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 6 at the visits indicated in Table 4 and Table 5.

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 after 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 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.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is Covance. Samples will be sent to the following addresses:

Covance Central Laboratory Services
c/o BML General Laboratory
1361-1, Matoba, Kawagoe City
Saitama, Japan 350-1101

Table 6. 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 transaminase (SGPT/ALT) Aspartate transaminase (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) eGFR$_J$ (MDRD modified)[c]	HBsAg[d] Anti-HCV Ab[d] Anti-HIV Ab[d] Opiates[d] Barbiturates[d] Amphetamines[d] Cocaine[d] Benzodiazepines[d] Alcohol[d] Phencyclidine[d] Propoxyphene[d] Methadone[d] Urine and Serum Human Chorionic Gonadotropin (hCG) for females[e] Follicle-Stimulating Hormone (FSH) (females)[d] HCV RNA Hepatitis B Panel[f] Hemoglobin A1C IL28B HCV genotype and subtype[d] Pharmacogenetic sample (optional) Alpha2-macroglobulin[g] Haptoglobin[g] Apolipoprotein A1[g] Hyaluronate[i] Protein electrophoresis (includes Gamma-globulin and total protein)[h]
Urinalysis		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Microscopic (reflex)		

a. Directly measured.
b. Performed only at Baseline.
c. eGFR calculated by the MDRD formula, modified for the Japanese population.
d. Performed only at Screening.
e. Pregnancy testing is not required for females of non-childbearing potential.
f. Performed for management of transaminase elevation (Section 6.1.7.4).
g. Component of FibroTest and collected only if needed during the Screening Period.
h. Component of Discriminant Score and 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. Additional urine pregnancy tests will be performed at all the visits indicated in Table 6 and Table 7. Arm B subjects will also have monthly urine pregnancy tests performed for a minimum of 6 months after the discontinuation or RBV, or according to the local RBV label and/or consistent with the local treatment guidelines for RBV. 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 Treatment Period and 30 days after study drugs are stopped must be recorded in the eCRF at each study visit indicated in Table 4 (Treatment Period). Thereafter, only medications taken for SAEs and treatment of HCV will be recorded in the eCRF at each study visit indicated in Table 5 (Post-Treatment Period).

Hepatitis and HIV Screen

HBsAg (hepatitis B surface antigen), anti-HCV Ab and anti-HIV Ab tests will be performed at Screening. The HIV Ab results will not be reported by the central laboratory to the clinical database.

Urine Screens for Drugs of Abuse

Urine specimens will be tested at the Screening Visit for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed in Table 6. Any positive result must be assessed for clinical significance, i.e., positive result is associated with documented short-term use or chronic stable use of a prescribed medication in that class.

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 (Discriminant Score, 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, New Inuyama 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 FibroScan® or liver 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 indeterminate FibroTest result ($0.48 < \text{result} < 0.75$), or conflicting FibroTest and APRI results (e.g., FibroTest ≤ 0.72, but APRI > 2 or FibroTest ≥ 0.73, but APRI ≤ 2) at Screening, a FibroScan® or liver 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. Subjects with indeterminate Discriminant Score (score = 0) at Screening, a FibroScan or liver biopsy can be performed during Screening to ascertain the presence or absence of cirrhosis.

Study Drug Diary

Subjects will be provided self-administration instructions and study drug diaries to record the exact date, time and number of tablets of study drug administration. On Study Day 1 the time of dosing will be recorded to the nearest minute by the site staff. The exact date, time and number of tablets of study drug taken will be recorded daily by the subjects between study visits. The exact date, time and number of tablets of the last 2 doses of study drug will be recorded to the nearest minute on the 2 days prior to the scheduled pharmacokinetic (PK) sample collection starting with the Week 1 Visit, as specified in Table 4. The site staff will record the information from the study drug diary for the last 2 doses of study drug into the eCRF. In the event the study drug diary is not available, the site may obtain dosing information via patient interview and record this information in the source notes.

To facilitate proper dosing of study drug before PK evaluation blood samples are taken the following procedures should be performed:

- The study coordinator should make sure the subject is given the dosing diary on the visit before the PK blood samples are taken.
- The investigator or designee will contact the subject by telephone approximately 2 days prior to the scheduled PK blood collection date to review the importance of proper study drug administration relative to the PK blood collection and documentation of dosing times on the study drug diary. Documentation of the date and time of the phone contact will be entered into source documentation.
- The subject should document on the study drug diary the exact date, time and number of tablets taken of the last 2 doses of study drug prior to the scheduled PK sampling. The completed study drug diary will be collected by the

investigator or designee on the day of the PK sampling and be kept as a record of dosage administration times in the eCRF.

Subjects will be required to bring back all study drug kits (even if empty) and the study drug diary cards to the study site at the study visits indicated in Table 4. Study drug compliance per the number of study drug tablets remaining in each kit will be recorded in the source and entered into the IRT system. Additional information regarding treatment compliance can be found in Section 5.5.6.

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 Table 4 and Table 5. 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 procedures or discussion of adverse events or any review of laboratory findings, including HCV RNA levels, at all other visits.

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 enrollment via the IRT system on Study Day 1.

Screening numbers will be unique 5-digit numbers and will begin with 20101 with the first three digits representing the investigative site, and the last two digits representing the subjects at that site. Enrolled subjects will keep their screening number as their subject number throughout the study. Subjects will be enrolled on Study Day 1 as described in Section 5.5.4 and will receive a separate unique 4-digit randomization number that will be recorded automatically in the eCRF through the IRT system. This 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 and SOF and RBV 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 and SOF and RBV. At each Study Drug Accountability Visit in Table 4, the overall number of tablets of ABT-493/ABT-530 or SOF and RBV remaining in each kit will be recorded in the source and entered in the IRT system along with the date of reconciliation.

HCV Genotype and Subgenotype

Plasma samples for HCV genotype and sub-genotype determination will be collected at Screening. Genotype and sub-genotype will be assessed using the Versant® Inno-LiPA Assay, version 2.0 or higher, used by the central lab. If the LiPA assay is unable to genotype a sample, its genotype will be determined by a Sanger sequencing assay by the central lab. Phylogenetic analysis of sequences will be performed by AbbVie to ascertain the HCV subtype.

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Table 4 and Table 5. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for this assay (regardless of genotype) are both 15 IU/mL.

HCV Resistance Testing Sample

A plasma sample for HCV resistance testing will be collected prior to dosing on Study Day 1 and at the study visits indicated in Table 4 and Table 5. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples 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 Table 4 and Table 5. Archive plasma samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, HCV RNA levels, 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 drug (i.e., ABT-493/ABT-530 and SOF plus RBV) tablets/capsules should be taken after 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 (Required, JPMA Category A)

One (required) 2 mL whole blood sample for Deoxyribonucleic acid (DNA) isolation will be collected from each subject on Study Day 1 for Interleukin 28B (IL28B) pharmacogenetic analysis. This sample will not be used for any testing other than IL28B genotypes. IL28B genotyping will be performed by the central laboratory. Any remaining DNA will be destroyed at the completion of the study.

Pharmacogenetic Sample (Optional, JPMA Category B)

A separate (optional) 4 mL whole blood sample for DNA isolation will be collected on Study Day 1 from each subject who consents to provide samples for pharmacogenetic analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

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 20 years.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of ABT-493, ABT-530, SOF and RBV and their possible metabolites will be collected by venipuncture at each study visit indicated below and in Table 4.

Subjects who do not participate in Optional Intensive PK sampling:

- At all Treatment Period visits, except for Study Day 1, a single (3 mL) blood sample will be collected without regard to the time of dosing.
- The date and time of blood sample collection and the two previous doses of the study drug from the study drug diary (see Section 5.3.1.1) 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 Study Day 1 and the Week 4 visit, subjects will have their dose administered by study site personnel after food. Blood samples will be collected on Study Day 1 at 2, 4 and 6 hours post-dose and at the Week 4 Visit immediately prior to dose (0 hour) and 2 and 4 hours post-dose.
  - 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) from the study drug diary (see Section 5.3.1.1) will be recorded to the nearest minute on the eCRF.
- At all other Treatment Period visits, a single blood sample will be collected without regard to the time of dosing.
  - 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 from the study drug diary (see Section 5.3.1.1).

A single (3 mL) blood sample will be collected from each subject at each time point (as applicable) for PK analysis in Arm A. Two separate (3mL) blood samples will be collected from each subject at each time point (as applicable) for PK analysis in Arm B.

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, ABT-530, SOF and RBV (and their possible metabolites) 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, ABT-530, SOF and RBV (and their possible metabolites) 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, SOF and RBV samples to the reference laboratories following separately provided instructions.

5.3.2.4 Measurement Methods

Plasma concentrations of ABT-493, ABT-530, SOF, GS-331007 and RBV when applicable, 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.

5.3.3 Efficacy Variables

Virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Study Day 1 through 24 weeks after completion of treatment.

5.3.3.1 Primary Variable

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

5.3.3.2 Secondary Variable

The secondary efficacy variables are on-treatment virologic failure and post-treatment relapse.

5.3.4 Resistance Variables

For all subjects receiving ABT-493/ABT-530, the variants at signature resistance-associated amino acid positions 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 ABT-493/ABT-530 who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid variants in available post-baseline samples identified by population or deep sequencing in comparison to the baseline sequence, 2) the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population or deep sequencing in comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral variants by population or deep sequencing.

5.3.5 Safety Variables

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

5.3.6 Pharmacokinetic Variables

Individual plasma concentrations of ABT-493, ABT-530, SOF, GS-331007 and RBV will be tabulated and summarized.

5.3.7 Pharmacogenetic Variables

IL28B status will be determined for each subject and analyzed as a possible 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 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 possibly contributing 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 the disease or drug response (including IL28B). Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. Pharmacogenetic analyses will be limited to studying response to the HCV therapy; no other analyses will be performed.

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 course of study drug administration, the subject prematurely discontinues, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 4 and Table 5. 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 persistence of resistant viral variants.

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 Treatment Period, the administration of ABT-493/ABT-530 to that subject may be continued after discussion with the AbbVie TA MD and the subject, if the benefit of continuing ABT-493/ABT-530 is felt to outweigh the potential risk. However, those subjects receiving the SOF plus RBV regimen (Arm B) who have a positive result on a pregnancy test or report becoming pregnant during the Treatment Period, must be notified to stop SOF plus RBV immediately. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3. The investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry.

5.4.1.1 Virologic Stopping Criteria

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 virologic stopping criterion has been confirmed. Subjects meeting virologic stopping criteria 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 until 24 weeks post-treatment.

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

Study drug (ABT-493/ABT-530) will be dispensed in the form of co-formulated tablets at the visits listed in Table 4. SOF and RBV will be dispensed in the form of tablets and capsules, respectively, at the visits listed in Table 4. Subjects will be instructed to take study drugs at the same time every day after 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, they will have their dose administered by study site personnel at these visits after food and having blood samples 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.

ABT-493/ABT-530 will be provided by AbbVie as 100 mg/40 mg co-formulated tablets. ABT-493/ABT-530 will be taken orally as 3 tablets once daily, which corresponds to ABT-493 300 mg/ABT-530 120 mg QD.

SOF will be provided by AbbVie as 400 mg tablets. SOF will be taken orally as 1 tablet once daily, which corresponds to 400 mg QD.

RBV will also be provided by the AbbVie for use in this study as 200 mg capsules. RBV should be dosed based on consideration of the subject's weight from the Study Day 1 Visit and their hemoglobin test results from the Screening Visit, according to the current approved local RBV label.

All study drugs should be taken after 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 Treatment Period or at the Premature D/C Visit from the 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 study drug and meet the virologic stopping criteria defined in Section 5.4.1.1 will be discontinued from treatment.

5.5.2 Identity of Investigational Products

Information about the study drugs to be used in this study is presented in Table 7.

Table 7. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
ABT-493/ABT-530	AbbVie	Oral	Tablet	100 mg/40 mg
SOF	Gilead	Oral	Tablet	400 mg
RBV	MSD	Oral	Capsule	200 mg

5.5.2.1 Packaging and Labeling

ABT-493/ABT-530 will be supplied in bottles containing 30 tablets. SOF will be supplied in bottles containing 28 tablets. RBV will be supplied in blister/carton boxes containing 140 capsules.

Each kit will be labeled as required per country requirements.

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

5.5.2.2 Storage and Disposition of Study Drugs

Study Drug	Storage Conditions
ABT-493/ABT-530 bottles	15° to 25°C (59° to 77°F)
SOF bottles	1° to 30°C (33.8° to 86°F)
RBV kits	1° to 30°C (33.8° to 86°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.

The randomization will be stratified by prior IFN-experience (naïve versus experienced) and Screening HCV RNA (< or ≥ 6 million IU/mL).

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

Subjects meeting the eligibility criteria will be enrolled as described in Section 5.3.1.1.

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 Study Day 1 Visit.

All three tablets of ABT-493/ABT-530 will be dosed together QD. SOF will be dosed QD. RBV should be dosed BID, e.g., 1 or 2 capsules taken in the morning, and 2 or 3 RBV capsules should be taken in the evening. All subjects should take all doses of study medications after food.

5.5.5 Blinding

This is an open-label study.

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 visit during the Treatment Period, 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 Table 4, 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 study drug 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. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in 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 Treatment Period. 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 kit of ABT-493/ABT-530, SOF or RBV the IRT system must be contacted and informed of the misplaced or damaged study drug. If the kit 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 kit, 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 Treatment Period, all original study drug kits (containing unused study drugs) will be returned to AbbVie (or designee). 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 kit 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

This is a multicenter, randomized, active-control, open label Phase 3 study in DAA treatment-naïve HCV GT2-infected Japanese subjects without cirrhosis, evaluating the safety and efficacy of the ABT-493/ABT-530 300/120 mg QD combination for 8 weeks of treatment.

Evaluation of an 8-week treatment duration in the current study is supported by efficacy data from Arm J in Part 2 of the ongoing Study M14-868 evaluating ABT-493 300 mg in combination with ABT-530 120 mg in GT2-infected patients without cirrhosis for 8 weeks, where preliminary data show that 53/54 (98%) of subjects achieved SVR_4. Also GT2-infected patients in Part 1 of Study M14-868 receiving ABT-493 300 mg and ABT-530 120 mg for 12 weeks demonstrate 96% SVR_{12} rate in subjects (i.e., 24/25 patients achieved SVR_{12} with no subjects experiencing virologic failure and one patient was lost-to-follow-up).

The primary objective of this study is to assess the efficacy and safety of 8 weeks of treatment with the combination regimen ABT-493/ABT-530 compared to SOF plus RBV in HCV GT2-infected subjects without cirrhosis. A comparative study utilizing an active control design provides an adequate assessment of the efficacy and safety of the combination of ABT-493 and ABT-530 compared to a standard of care regimen, while also providing a potentially efficacious or approved regimen to all participating subjects.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA assays for the primary and secondary efficacy endpoints are standard and validated.

5.6.3 Suitability of Subject Population

This study will enroll subjects with HCV GT2 infection who are naïve or IFN experienced (with or without RBV) to HCV treatment, without cirrhosis. The sample size of 120 subjects is sufficient to power the non-inferiority efficacy comparison while limiting the number of subjects as only approximately 30% of the Japanese HCV-infected population has GT2 infection.

5.6.4 Selection of Doses in the Study

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. The dose of SOF plus RBV was selected based on its approval for use in Japan.

5.6.4.1 ABT-493, ABT-530, SOF and RBV Doses

The 300 mg ABT-493 and 120 mg ABT-530 doses were selected to provide one regimen for all HCV genotypes that is safe and achieves drug exposure coverage that maximizes the chance to prevent the selection of resistant virus and achieves the highest possible SVR rates. Further detailed rationale is provided below:

- ABT-493/ABT-530 doses lower than 300 mg/120 mg showed suboptimal SVR rate in Phase 2 GT1 and GT3-infected subjects: in Part 1 of Study M14-867 in all 40 GT1-infected subjects who received ABT-493 200 mg and ABT-530 120 mg (including 15 PR-null responders) achieved SVR_{12}. One subject (treatment-naive) in the ABT-493 200 mg and ABT-530 40 mg arm had virological relapse at Post-Treatment Week 4. In Part 1 of Study M14-868 in GT3-infected subjects, both ABT-530 doses of 40 mg and 120 mg were evaluated in combination with ABT-493: 2 subjects experienced virologic

failure in the ABT-530 40 mg arm and 3 subjects experienced virologic failure in the ABT-530 120 mg arm. For ABT-493, in the GT3 arms of Part 1 of Study M14-868, 2 subjects (1 treatment-naïve and 1 PR-experienced) had virologic 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. For GT2, ABT-493 300 mg and ABT-530 120 mg have been administered to 54 subjects and no subject had virologic failure. Across different HCV genotypes 1 to 6, ABT-493 300 mg + ABT-530 120 mg dose demonstrated potent in vitro efficacy with high SVR rates of 96% – 100%. Since the objective is to develop one dose across all genotypes, the proposed dose for treatment of GT-2 infection is the fixed-dose combination of ABT-493/ABT-530 (300/120 mg).

- 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.
- In Phase 1 studies, no ethnic difference was observed in ABT-493 and ABT-530 exposures for Japanese, Han Chinese and Caucasian subjects which supports using the same doses in the Japanese subjects as those in the Western studies.

For Phase 3 studies, s film-coated co-formulated bilayer tablet of ABT-493 and ABT-530 will be used. Preliminary pharmacokinetic results of the Phase 3 bilayer tablet administered under fasting conditions showed approximately 35% to 56% lower bioavailability compared to the Phase 2 formulation at the ABT-493 300 mg and ABT-530 120 mg. When the Phase 3 bilayer tablet was administered under non-fasting

conditions, exposures became comparable to the Phase 2 formulations. Hence, in Phase 3 studies, the ABT-493/ABT-530 bilayer tablet should be administered after food.

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

The dose of SOF plus RBV (SOF 400 mg per day, RBV 600 to 1000 mg per day based on body weight) to be administered in the study is the approved dose for HCV GT2-infected subjects in Japan.

The maximum dose of SOF will not exceed 400 mg per day for 12 weeks and the maximum dose of RBV will not exceed 1000 mg per day for 12 weeks.

5.6.4.2 Rationale for Duration Selections

Evaluation of an 8-week treatment duration for ABT-493/ABT-530 in the current study is supported by preliminary data from the ongoing Phase 2b Study M14-868 Part 2. In Arm J of Part 2 evaluating ABT-493 300 mg + ABT-530 120 mg for 8 weeks in GT2-infected subjects without cirrhosis, 53 out of 54 (98%) subjects achieved SVR_4 (1 subject lost to follow up) and to date, 23 out of 23 (100%) achieved SVR_{12}. The one subject that did not achieve SVR_4 was lost to follow-up and did not experience virologic failure.

For the active control arm, SOF plus RBV is approved for 12-week treatment duration in HCV GT2-infected subjects.

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 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 variants 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, in Phase 2b Study M14-867 Part 1 evaluating the combination of ABT-493 and ABT-530 in GT1-infected subjects without cirrhosis for a 12-week duration, 79 subjects have reached post-treatment Week 12 as of 22 May 2015. Among these 79 subjects, 1 subject experienced virologic failure, and preliminary sequencing results indicated that treatment-emergent NS5A RAVs were detected at the time of failure in this subject. These results support the prediction that the risk of development of resistance-associated variants 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 the Sponsor (Section 6.2.2). For adverse events, please refer to Section 6.1. 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 adverse event 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 adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse

event. 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, [meets protocol specific criteria (see Section 6.1.7 regarding toxicity management)] and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event 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 adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event 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 serious adverse event.

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 serious adverse events 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 adverse event 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 adverse events. 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 Adverse Events (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 adverse event to the use of study drug:

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

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.

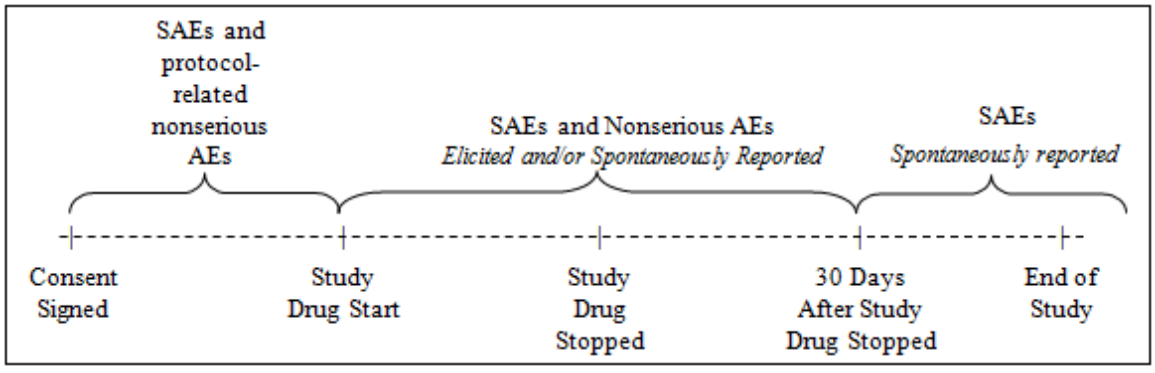
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related non-serious adverse events (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 adverse events 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 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events 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 serious adverse event.

Email: [redacted]

FAX to:

For safety concerns, contact the Japan Medical Science Group at:

Medical Science Group
[redacted]
Tokyo, 108-6302

[redacted]

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

Primary TA MD:

Alternate TA MD:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (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: 

In Japan, the principal investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

6.1.6 Pregnancy

Subjects and their partners should avoid pregnancy starting with Screening and through 30 days after stopping study drugs for Arm A and 6 months after stopping study drugs for Arm B.

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. The investigator should discuss the potential risks versus benefits with the subject and contact the AbbVie TA MD to determine if the subject should continue or discontinue ABT-493/ABT-530. Administration of ABT-493/ABT-530 may be continued after approval by the AbbVie TA MD, if the benefit of continuing therapy is felt to outweigh the risk (Section 5.4.1). However, in the event of pregnancy, administration of SOF plus RBV must be discontinued immediately. If study drug is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

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 with ABT-493/ABT-530 or through the duration of the study (or per local RBV label) for treatment with SOF plus RBV. The investigator is encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry, if RBV is included within the regimen.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

The Toxicity Management guidance applies to all subjects enrolled in both arms of the study with additional guidance provided in sections addressing hemoglobin (Section 6.1.7.4) and creatinine clearance (Section 6.1.7.6) for subjects in Arm B. For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator. The table of clinical toxicity grades for evaluating laboratory abnormalities is provided in Appendix C. This table should be used in determination of the appropriate toxicity management as discussed in Section 6.1.7.1 and Section 6.1.7.2. The toxicity management guidelines outlined below (Sections 6.1.7.1 through 6.1.7.5) should be followed throughout the Treatment Period of the study.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the investigator or the Sponsor as having a "reasonable possibility" of being related to the study drugs (Section 6.1.7.4). A toxicity is deemed "clinically significant" based on the medical judgment of the investigator. Laboratory abnormalities will be managed as deemed clinically appropriate by the investigator until resolved.

Study drugs should not be interrupted for toxicity management for more than 7 consecutive days. If study drugs needs to be interrupted for more than 7 consecutive days, consideration should be given to discontinue the subject and the AbbVie TA MD should be contacted. The appropriate study drug interruption for toxicity management eCRF should be completed.

The toxicity management guidelines below should be followed.

6.1.7.1 Grade 1 or 2 Laboratory Abnormalities or Adverse Events

Subjects who develop a study drug-related (reasonable possibility) Grade 1 or 2 adverse event or Grade 1 or 2 laboratory abnormality [other than those discussed separately in the Toxicity Management Section for ALT elevations and bilirubin elevations (Section 6.1.7.5 and Section 6.1.7.7) and hemoglobin and creatinine clearance decreases

(Section 6.1.7.4 and Section 6.1.7.6), may continue study drugs with appropriate medical management and follow-up per study protocol.

6.1.7.2 Grade 3 or 4 Laboratory Abnormalities

If a subject experiences a Grade 3 or greater laboratory parameter during the study (other than those discussed separately in the Toxicity Management Section for ALT and bilirubin elevations [Section 6.1.7.5 and Section 6.1.7.7] and hemoglobin and creatinine clearance decreases for subjects in Arm B [Section 6.1.7.4 and Section 6.1.7.6]), the abnormal laboratory test should be repeated. If the Grade 3 or greater abnormality is confirmed, the study drugs should be interrupted until the laboratory parameter has returned to its baseline level or stabilized. The study drugs can be restarted if the laboratory parameter reaches baseline grade or Grade 1 (whichever is higher) within 7 days of study drug interruption. If study drugs are interrupted and restarted and the laboratory value rises to Grade 2+ or a grade higher than baseline, then study drugs should be permanently discontinued, unless approval for continuing study drugs is obtained from the AbbVie TA MD. If the abnormality does not reach Grade 1 or the baseline grade within 7 days of interruption, the study drugs should be permanently discontinued.

If the investigator considers that the confirmed Grade 3 or greater laboratory parameter is not clinically significant or is not related to study drug and therefore study drug interruption or discontinuation is not warranted, study drugs can be continued with approval of the AbbVie TA MD.

Grade 3 or higher elevations in uric acid, phosphorous, total cholesterol, triglycerides, or glucose (in subjects with a history of diabetes) should be managed medically as appropriate and do not require confirmation or study drug interruption. However, study drug may be interrupted if deemed necessary by the investigator.

6.1.7.3 Grade 3 or 4 Adverse Event or Serious Adverse Event

If a subject experiences a Grade 3 or 4 adverse event or a serious adverse event that the investigator considers to have a reasonable possibility of relationship to study drug, the following should occur:

- Study drugs should be discontinued,
- The AbbVie TA MD should be contacted to discuss the event,
- The subject should be monitored until event resolution.

If the investigator believes that the drug-related (reasonable possibility) Grade 3 or 4 adverse event or serious adverse event can be managed medically without permanent discontinuation, then the AbbVie TA MD should be contacted to discuss continued study drug administration with medical management.

If a subject experiences a Grade 3 or 4 adverse event or serious adverse event that is considered unrelated (no reasonable possibility) to the study drugs, then study drugs may be continued.

If study drug interruption is deemed necessary for clinical management, the interruption should not exceed 7 days. If study drug interruption is required for longer than 7 days, then study drugs should be permanently discontinued.

The investigator should ensure that all serious adverse events are reported to AbbVie within 24 hours of awareness. Serious adverse event follow-up information, including associated dose interruptions (or discontinuations), must be reported to the AbbVie within 24 hours of awareness by entering updated SAE information into the appropriate eCRFs. Grade 3 or 4 adverse events and any associated dose interruptions (or discontinuations) should be entered into the appropriate eCRFs.

6.1.7.4 Management of Decreases in Hemoglobin

For subjects in Arm A (not receiving RBV), hemoglobin decreases should be managed according to Toxicity Grade based on the guidance in Section 6.1.7.1 and Section 6.1.7.2.

For subjects in Arm B (receiving SOF and RBV), hemoglobin decreases should be managed according to Table 8.

Decreases in hemoglobin are a well characterized side effect of ribavirin exposure. If a subject receiving the standard dose of ribavirin experiences a hemoglobin decrease meeting one of the criteria outlined in Table 8, a confirmatory test should be performed. If the hemoglobin decrease is confirmed, the management guidelines in Table 8 should be followed. Management will be different for subjects without a history of known cardiac disease and subjects with known cardiac disease. Subjects experiencing decreases in hemoglobin that do not meet the criteria outlined in Table 8 may need hemoglobin evaluations at more frequent intervals at the discretion of the investigator.

Use of hematologic growth factors (such as erythropoietin or filgrastim) or blood transfusions are permitted at the discretion of the investigator. Management of hematologic growth factor therapy is the responsibility of the Investigator, and growth factors will not be provided by AbbVie.

Alternate management of hemoglobin decreases outside of these criteria is permitted with approval of the AbbVie TA MD.

Table 8. Ribavirin Dose Modification Guidelines in Management of Hemoglobin Decreases

Laboratory Parameter	Value	Ribavirin
Hemoglobin level (patients without current or a history of heart disorder	< 10 g/dL	Reduce dosage 600 mg/day → 400 mg/day 800 mg/day → 600 mg/day 1000 mg/day → 600 mg/day
	< 8.5 g/dL	Discontinue[a]
Hemoglobin level (patients with current or a history of heart disorder[b]	< 10 g/dL, or a decrease of ≥ 2 g/dL from baseline persisting for 4 weeks during treatment with a reduced dose	Reduce dosage 600 mg/day → 400 mg/day 800 mg/day → 600 mg/day 1000 mg/day → 600 mg/day
	< 8.5 g/dL or < 12g/dL after 4 weeks of treatment with a reduced dose	Discontinue[a]

a. If ribavirin is discontinued, sofosbuvir also must be discontinued to avoid sofosbuvir monotherapy.

b. When REBETOL is administered to patients with current or a history of heart disorder, the treating physician should consider reducing the dose of REBETOL if a decrease of ≥ 2 g/dL from baseline persists for 4 weeks despite a current Hb level of ≥ 10 g/dL and should consider discontinuing REBETOL if the Hb level is less than 12 g/dL (albeit 8.5 g/dL or higher) after 4 weeks of treatment with a reduced dose (see "Careful administration").

Notes: Reduce RBV daily dose in accordance with local RBV prescribing information/product label.

Monitor neutrophil and platelet counts in accordance with the local RBV prescribing information/product label.

If the abnormality is reversed, RBV may be restarted at the discretion of the investigator and in accordance with local RBV prescribing information/product label.

6.1.7.5 Management of Increases in ALT

If a subject experiences a post-baseline increase in ALT to ≥ 5 × ULN and 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:

- Evaluate for alternate etiology of ALT elevation; document in the source and update the medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate (e.g., hepatitis B panel).*
- 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.
  - Onset of symptoms/signs of hepatitis.
  - At the discretion of the investigator.

* If another cause is identified based on additional testing, study drugs may be continued and subject should be managed as medically appropriate.

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

6.1.7.6 Creatinine Clearance

If calculated creatinine clearance (by Cockcroft-Gault formula) is confirmed to have decreased to < 50 mL/minute, medical evaluation should include a full review of current medications, including those taken on an as needed basis, those which are sold over the counter and any dietary and herbal supplements, and appropriate dose reduction or discontinuation based on impaired renal function should be done (if applicable). For subjects in Arm B, if the investigator considers ribavirin to be the cause of decreased creatinine clearance < 50 mL/minute, then consideration should be given to discontinue both ribavirin and sofosbuvir. However, the decision to discontinue ribavirin and sofosbuvir should be made only after discussion of the risks versus benefits of discontinuation with the AbbVie TA MD. The investigator should also consider whether concomitant medications may have contributed to the decrease in creatinine clearance, and whether discontinuation or substitution of the concomitant drug might be needed. Alternative management of RBV continuation (including dose reduction of ribavirin) in the setting of reduced renal function will require approval of the AbbVie TA MD.

In addition, the following should occur:

- For subjects in Arm B, SOF and RBV local labels must be checked for any SOF and/or RBV dose adjustments.
- Additional work-up (e.g., CPK, urine albumin) should be done as clinically indicated.

The Investigator should ensure that any concomitant medication changes, RBV dose reductions, and study drug discontinuations, as well as consequent related adverse events are entered into the appropriate eCRFs.

6.1.7.7 Management of Grade 3 or Greater Elevations of Total Bilirubin

All grade 3 or greater results for total bilirubin should be fractionated for direct and indirect bilirubin and repeated. If there is a confirmed Grade 3 total bilirubin, these results should be discussed with the AbbVie TA MD and consideration given to discontinuation of study drugs in the subject. The decision to discontinue study drugs should take into consideration the clinical status of the subject, including any clinical signs/symptoms reported by the subject as well as laboratory results, and will be at the clinical discretion of the investigator.

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

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 the Sponsor 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 the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events 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 along with the following AbbVie Clinical Monitors:

Primary Contact: Alternate Contact:

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.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will occur after all subjects have completed the PT Week 12 Visit or prematurely discontinued the study. The data for the primary analysis will be locked after appropriate data cleaning. Data after PT Week 12 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 αlevel of 0.05.

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, unless otherwise specified. Sensitivity analyses of the primary endpoint, will be performed on the modified ITT (mITT) population to exclude subjects not of GT2 according to the central laboratory or according to phylogenetic analyses (mITT-GT), and on the mITT-GT population further modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-VF).

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data) and the 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

Demographics and baseline characteristics will be summarized for all subjects in the ITT population for each treatment arm. Demographics include age, weight, height, BMI, gender, race, and ethnicity. 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 genotype and subtype, IL28B genotype, prior HCV treatment history, baseline HCV RNA level, fibrosis stage (F0 – F1, F2, F3]), baseline homeostasis model of assessment – insulin resistance (HOMA-IR), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, former injection drug user (yes, within last 12 months; yes, more than 12 months ago; or no), use of stable opiate substitution, history of diabetes, history of bleeding disorders, history of depression or bipolar disorder, and history of cardiovascular disease.

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 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. Compliance will be calculated for each subject for each tablet type, and summarized with the mean, median, standard deviation, minimum, and maximum. A subject is considered to be compliant if the percentage is between 80% and 120%. The percentage of compliant subjects will be summarized for each treatment arm and tablet/capsule type.

8.1.2 Efficacy

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

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 which has lower limit of quantification (LLOQ) and lower limit of detection (LLOD) of 15 IU/mL. The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 15 IU/mL that are HCV RNA detected or HCV RNA not detected. HCV RNA ≥ LLOQ are all quantifiable values.

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

8.1.2.1 Primary Efficacy Endpoints

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

The primary efficacy endpoint is:

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

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

8.1.2.2 Secondary Efficacy Endpoints

The following secondary endpoints will be summarized:

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

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

For the analysis of relapse and reinfection, completion of treatment is defined as any subject assigned to the12-week treatment with study drug duration of 77 days or greater; or any subject assigned to the 8-week treatment with study drug duration of 52 days or greater. Subjects with probable reinfection based on HCV sequencing or differing post-treatment HCV genotype or subtype will be summarized separately from relapse.

The percentage of subjects with on-treatment virologic failure and post-treatment relapse will be summarized for each treatment arm. Two-sided 95% confidence intervals will be provided for rates within treatment arms and for the difference between arms (Arm A minus Arm B) using Wilson's score confidence intervals.

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

8.1.2.3 Sensitivity Analysis

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

- A two-sided 95% confidence interval for the SVR_{12} rates within each arm will be calculated using a Wilson score interval.
- The percentage of subjects achieving SVR_{12} will be compared using a logistic regression model with treatment arm as a factor, and baseline $\log_{10}$ HCV RNA level, HCV genotype 2 subtype, and prior HCV treatment history as coviariates.
- The difference in SVR_{12} rates (Arm A minus Arm B) will be analyzed using a stratum-adjusted Mantel-Haenszel (MH) proportion with a continuity correction for variance, adjusting for both of the randomization stratum (described in Section 8.3).
- A two-sided 95% confidence interval for the difference in SVR_{12} rates (Arm A minus Arm B) will be calculated using a Wilson score interval.

The above analyses will be performed on the ITT, mITT-GT, and mITT-GT-VF populations, as applicable.

8.1.2.4 Subgroup Analysis

To evaluate the impact of various characteristics on treatment effect, subgroup analyses will be performed for the primary efficacy endpoint. Within each subgroup, the percentage of subjects with SVR_{12} within each arm and the difference between treatment arms in the percentage of subjects with SVR_{12} will be calculated, as will the corresponding two-sided 95% Wilson score confidence intervals. A test of homogeneity will be conducted (Zelen's exact test) to evaluate whether differences between treatment arms are consistent across subgroups (i.e., confidence intervals for the difference in SVR_{12} rates will not be compared to the non-inferiority margin due to the decreased sample size in each subgroup). The following subgroups will be analyzed:

- HCV genotype 2 subtype;
- Prior HCV treatment history;
  - For treatment experienced subjects, type of non-response to previous treatment;
- IL28B genotype;
- Sex;
- Age;
- Race;
- Ethnicity;
- 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;
- AST/ALT ratio;
- History of diabetes;
- History of bleeding disorders;
- History of depression or bipolar disorder;
- History of cardiovascular disease;
- Former injection drug user;
- Subject on stable opiate substitution;
- Compliant to study drug.

Further details about subgroup analysis will be described in the statistical analysis plan.

8.1.2.5 Additional Efficacy Endpoints

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

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects with SVR_4;
- The percentage of subjects with SVR_{24};
- The reasons for not achieving SVR_{12} and the reasons for not achieving SVR_{24}

In the above analyses for SVR and reasons for not achieving SVR, the percentage of subjects in each treatment arm with a two-sided 95% Wilson score confidence interval will be summarized.

8.1.3 Patient Reported Outcomes

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

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

8.1.4 Resistance Analyses

The DNA encoding NS3 amino acids 1 – 181 and NS5A amino acids 1 – 215 will be sequenced by population or deep sequencing for analysis of available baseline samples from the SVR-achieving subjects in Arm A. For subjects in Arm A who do not achieve SVR_{12}, full length NS3/4A and NS5A genes from their available baseline and virologic failure (VF)/discontinuation 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. For subjects who experience VF in Arm B (on-treatment VF or post-treatment relapse), the full length NS5B gene from their available baseline and VF samples will be sequenced by population or deep sequencing. An appropriate prototypic reference sequence will be used for comparison with sequences from subject 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 VF or treatment discontinuation is < 1000 IU/mL, the sample closest in time after VF/discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used. Included time points for analyses on available samples from subjects in Arm A who do not achieve SVR_{12} are 1) the sample closest in time after VF/discontinuation with an

HCV RNA level of ≥ 1000 IU/mL, and 2) 24 weeks post-DAA treatment, provided that resistance-associated variants were detected by either population or deep sequencing at the time of VF/discontinuation. The included time point for analyses on available samples from subjects in Arm B who experience VF is the sample closest in time after VF with an HCV RNA level of ≥ 1000 IU/mL.

The following definitions will be used in the 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: an amino acid variant in a post-baseline time point sample that was not detected at baseline in the subject.
- Enriched variant: a post-baseline variant that is enriched by at least 20% relative to its prevalence in the corresponding baseline sequence (post-baseline % – baseline % ≥ 20) by deep sequencing.
- Treatment-emergent variant: A post-baseline variant or an enriched variant.
- Emerged variant: a treatment-emergent variant that is observed in 2 or more subjects of the same HCV subtype.

The following baseline analyses will be performed:

The HCV amino acid sequence as determined by population or deep sequencing of available baseline samples from subjects in Arm A 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 impact of baseline variants on treatment outcome for subjects in Arm A will be assessed as follows: for each variant, the SVR_{12} rate will be calculated for subjects with and for subjects without the variant, and the 2 rates will be compared using

Fisher's exact test. The analyses will be grouped by baseline variant and prevalence of each variant within a subject's viral population, HCV subtype, and DAA target (NS3 or NS5A).

For subjects in Arm B who experience VF, a listing by subject of all baseline variants relative to prototypic reference sequence at signature resistance-associated amino acid positions will be provided for NS5B.

The following analyses will be performed for subjects in Arm A who do not achieve SVR_{12} 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 VF or treatment discontinuation 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 treatment-emergent variants detected by population or deep sequencing relative to the baseline amino acid sequences will be provided for each DAA target (NS3 and NS5A). In addition, listings by subject of all variants (by population or deep sequencing) at signature resistance-associated amino acid positions relative to the appropriate prototypic reference amino acid sequences 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 variants are not detected by either population or deep sequencing in a given target for a subject at the time of failure/discontinuation, then that target may not be sequenced in subsequent samples from that subject.

The following will be provided for subjects in Arm B who experience VF and have post-baseline resistance data available:

A listing by subject of all treatment-emergent variants at signature resistance-associated amino acid positions in NS5B relative to the baseline amino acid sequence.

Phylogenetic analysis will be conducted on HCV sequence from available baseline samples from all subjects in order to accurately determine their subtype. The resulting subtype information will be presented in summaries of baseline characteristics and efficacy subgroup analyses.

8.1.5 Safety

All subjects who receive at least one dose of study drug will be included in the safety analyses.

8.1.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects in each arm with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between arms using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug also will be provided. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade for the severity grade table and the most related 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 tests will be summarized by arm at each visit. The baseline value will be the last non-missing measurement prior to the initial dose of study drug. Mean changes from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized and the between-arm comparison will be performed using contrasts within an ANOVA model with treatment arm as the factor.

Laboratory data values will be categorized as low, normal, or high based on reference ranges of the laboratory used in this study. The number and percent of subjects who experience post-baseline shifts in clinical laboratory values from low/normal to high and high/normal to low based on the normal range will be summarized by arm.

In addition, the number and percentage of subjects with post-baseline values meeting pre-specified criteria for Potentially Clinically Significant (PCS) laboratory values or toxicity grades will be summarized by arm. The between-arm comparison will be performed on the percentage of subjects with laboratory abnormalities (PCS or by toxicity grade) for each parameter using Fisher's exact tests.

8.1.5.3 Vital Signs Data

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each post-baseline visit, including Final Treatment Visit, will be summarized descriptively by arm and the between arm comparison will be performed 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 PCS vital signs values will be summarized. The between-arm comparison of the percentage of subjects experiencing a value meeting the criteria will be performed using Fisher's exact tests.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Individual plasma concentrations of ABT-493, ABT-530, SOF, RBV and GS-331007 will be tabulated for each subject and each arm. Values for pharmacokinetic parameters of

ABT-493, ABT-530, SOF, RBV and GS-331007 will be tabulated for each subject who participates in Optional Intensive PK sampling. Individual plasma concentrations and pharmacokinetic parameters of possible metabolites of ABT-493, ABT-530, SOF (other than GS-331007) and RBV may be tabulated and summarized if measured and sufficient levels of metabolites are observed. 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.

8.1.7 Justification of Non-Inferiority Margin for SVR_{12}

To establish a threshold for demonstrating non-inferiority to the current standard of care, SOF plus RBV, a margin of 10% is used. The 10% margin is similar to the margin of 10.5% used in previous clinical trials of first-generation interferon-free regimens, based on the higher SVR rates provided by the current standard of care. The 10% margin is considered to be an appropriate potential loss of efficacy given that the current regimen reduces the duration of treatment to 8 weeks and eliminates the need for RBV.

8.2 Determination of Sample Size

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

With 80 subjects in the ABT-493/ABT-530 8-week arm (Arm A) and 40 subjects in the SOF plus RBV 12 week arm (Arm B) and assuming that 96% of the subjects in Arm A achieve SVR_{12} and 95% of subjects in Arm B (Table 1) achieve SVR_{12}, this study has > 80% power to demonstrate non-inferiority of the ABT-493/ABT-530 8-week treatment arm compared to the active control in SVR_{12} rate (i.e., a two-sided 95% lower confidence bound for the difference above the non-inferiority margin of –10%).

8.3 Randomization Methods

Approximately 120 subjects meeting all eligibility criteria will be randomized in a 2:1 ratio into Arms A and B and randomization will be stratified by prior IFN-experience (naive versus experienced) and Screening HCV RNA (< or ≥ 6 million IU/mL).

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.

The optional samples for intensive PK analyses and sample for optional pharmacogenetic analysis will only be collected if the subject has voluntarily signed and dated the a intensive PK section of the main ICF and a separate pharmacogenetic informed consent, respectively, 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 informed consent must be signed before the optional pharmacogenetic sample is collected and testing is performed. If the subject does not consent to the optional intensive PK analyses and/or optional pharmacogenetic testing, it will not impact the subject's participation in the study.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating 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 research that may be done using optional pharmacogenetics 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 subject nor the investigator will be informed of individual optional pharmacogenetic 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 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 Director of the Site in Japan and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Director of the Site in Japan and AbbVie. The investigator will provide a final report to the Director of the Site following conclusion of the study. Upon being provided the report, the Director of the Site will notify AbbVie or their representative and the IEC/IRB of the conclusion of the study in Japan.

The Director of the Site in Japan must retain any records related to the study according to local requirements. If the Director of the Site in Japan 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 and the product inserts for sofosbuvir and ribavirin.
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, Open-Label, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults with Genotype 2 Chronic Hepatitis C Virus Infection (CERTAIN-2)
Protocol Date:	17 June 2016

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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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]		Clinical
		Clinical
		CMC Group
		Clinical
		Pharmacokinetics
		Clinical
		Clinical
		Statistics
		Bioanalysis

Appendix C. Clinical Toxicity Grades

Clinical Toxicity Grades for HCV Studies[1,2]				
	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
HEMATOLOGY				
ABSOLUTE NEUTROPHIL COUNT DECREASED	<LLN – 1500/mm3 <LLN – 1.5 × 10e9/L	<1500 – 1000/mm3 <1.5 – 1.0 × 10e9/L	<1000 – 500/mm3 <1.0 – 0.5 × 10e9/L	<500/mm3 <0.5 × 10e9/L
EOSINOPHIL COUNT INCREASED	650-1500 cells/mm3	1501-5000 cells/mm3	>5000 cells/mm3	Hypereosinophilic
HEMOGLOBIN DECREASED	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L
INTERNATIONAL NORMALIZED RATIO (INR), INCREASED	>1 – 1.5 × ULN	>1.5 – 2 × ULN	>2 × ULN	
LYMPHOCYTE COUNT DECREASED	<LLN – 800/mm3 <LLN × 0.8 – 10e9/L	<800 – 500/mm3 <0.8 – 0.5 × 10e9/L	<500 – 200 mm3 <0.5 – 0.2 × 10e9/L	<200/mm3 <0.2 × 10e9/L
PLATELETS DECREASED	<LLN – 75,000/mm3 <LLN – 75.0 x 109 /L	<75,000-50,000/mm3 <75.0 – 50.0 x 109 /L	<50,000-25,000/mm3 <50.0 – 25.0 x 109 /L	<25,000/mm3 <25.0 x 109 /L
PTT	>1 – 1.5 × ULN	>1.5 – 2 × ULN	>2 × ULN	
WHITE BLOOD CELL COUNT DECREASED	<LLN – 3000/mm3 <LLN – 3.0 × 10e9/L	<3000 – 2000/mm3 <3.0 – 2.0 × 10e9/L	<2000 – 1000/mm3 <2.0 – 1.0 × 10e9/	<1000/mm3 <1.0 × 10e9/L
WHITE BLOOD CELL COUNT INCREASED	10,800 – 15,000 cells/mm3	>15,000 – 20,000 cells/mm3	>20,000 – 25,000 cells/mm3	>25,000 cells/mm3
CHEMISTRIES				
ALBUMIN, SERUM, LOW	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	
BILIRUBIN, HIGH	>ULN – 1.5 × ULN	>1.5 – 3.0 × ULN	>3.0 – 10.0 × ULN	>10.0 × ULN
BUN	1.25-2.5 × ULN	>2.5 -5.0 × ULN	>5 -10.0 × ULN	>10 × ULN
CALCIUM, SERUM LOW	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
CALCIUM, SERUM HIGH	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
CALCIUM, IONIZED, LOW	<LLN – 1.0 mmol/L	<1.0 – 0.9 mmol/L	<0.9 – 0.8 mmol/L	<0.8 mmol/L
CALCIUM, IONIZED, HIGH	>ULN – 1.5 mmol/L	>1.5 – 1.6 mmol/L	>1.6 – 1.8 mmol/L	>1.8 mmol/L

Clinical Toxicity Grades for HCV Studies
v1.1; 08June2009

Clinical Toxicity Grades for HCV Studies (Continued)				
	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
CHOLESTEROL HIGH	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
CREATININE	1.5 – 1.7 mg/dL	1.8 – 2.0 mg/dL	2.1 – 2.5 mg/dL	>2.5 mg/dL or requires dialysis
GLUCOSE, SERUM, LOW	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L
GLUCOSE, SERUM, HIGH (Fasting)	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis
MAGNESIUM, SERUM, LOW	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L
MAGNESIUM, SERUM, HIGH	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L		>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L
PHOSPHATE, SERUM, LOW	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L
POTASSIUM, SERUM, LOW	<LLN – 3.0 mmol/L		<3.0 – 2.5 mmol/L	<2.5 mmol/L
POTASSIUM, SERUM, HIGH	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L
PROTEIN, SERUM, LOW	5.5 – 6.0 g/dL	<5.5 – 5.0 g/dL	<5.0 g/dL	
SODIUM, SERUM, LOW	<LLN – 130 mmol/L		<130 – 120 mmol/L	<120 mmol/L
SODIUM, SERUM, HIGH	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L Hospitalization may be indicated	>160 mmol/L
TRIGLYCERIDES HIGH (fasting)	150-300 mg/dL; 1.71 – 3.42 mmol/L	>300-500 mg/dL; >3.42-5.7 mmol/L	>500-1000 mg/dL; >5.7 – 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
URIC ACID, SERUM, HIGH	7.5 – 10.0 mg/dL	10.1-12.0 mg/dL	12.1-15.0 mg/dL	>15.0 mg/dL

Clinical Toxicity Grades for HCV Studies
v1.1; 08June2009

Clinical Toxicity Grades for HCV Studies (Continued)				
	GRADE 1 TOXICITY	**GRADE 2 TOXICITY**	**GRADE 3 TOXICITY**	**GRADE 4 TOXICITY**
ENZYMES				
ALT/SGPT	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN;	>5.0 – 20.0 x ULN	>20.0 x ULN
AST/SGOT	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN;	>5.0 – 20.0 x ULN	>20.0 x ULN
ALKALINE PHOSPHATASE	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AMYLASE	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
LIPASE	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN

1 Adapted from the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 (CTCAE)
2 Used for all HCV development compounds

Clinical Toxicity Grades for HCV Studies
v1.1; 08 June 2009

Appendix D. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency Contact:	Urgent contact during business hours:	Urgent contact after business hours (at night or on holidays):
	[redacted]	[redacted]

Has been changed to read:

Sponsor/Emergency Contact:	Urgent contact during business hours:	Urgent contact after business hours (at night or on holidays):
	[redacted]	[redacted]

Section 1.2 Synopsis
Subsection AbbVie Inc.
Previously read:

AbbVie Inc.

Has been changed to read:

AbbVie GK

Section 1.2 Synopsis
Subsection Phase of Development:
Add: new subsection text

3

Section 1.2 Synopsis
Subsection Methodology:
Heading "Treatment Period"
Second paragraph previously read:

The randomization will be stratified by prior IFN-experience (naïve versus experienced) and baseline HCV RNA (< or ≥ 6 million IU/mL).

Has been changed to read:

The randomization will be stratified by prior IFN-experience (naïve versus experienced) and Screening HCV RNA (< or ≥ 6 million IU/mL).

Section 5.1 Overall Study Design and Plan: Description
Fourth paragraph, last sentence previously read:

The randomization will be stratified by prior IFN-experience (naive versus experienced) and baseline HCV RNA (< or ≥ 6 million IU/mL).

Has been changed to read:

The randomization will be stratified by prior IFN-experience (naive versus experienced) and Screening HCV RNA (< or ≥ 6 million IU/mL).

Section 5.2.3.1 Prior HCV Therapy
Add: new last sub-bullet

Unknown: subject received a prior treatment course and reason for not achieving SVR is unknown.

Table 4. Treatment Period
Activity "Vital Signs, Weight, Waist Circumference, Height[e]" previously read:

Vital Signs, Weight, Waist Circumference, Height[e]

Has been changed to read:

Vital Signs, Weight, Waist Circumference,[e] Height[e]

Section 5.3.1.1 Study Procedures
Subsection Medical History
First sentence previously read:

A complete medical history, including history of alcohol, tobacco and nicotine-containing product use, will be taken at Screening.

Has been changed to read:

A complete medical history, including history of alcohol, tobacco and illicit/illegal drug use, will be taken at Screening.

Section 5.3.1.1 Study Procedures
Subsection Hepatitis and HIV Screen
Delete: second and third sentence

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.

Section 5.3.2.1 Collection of Samples for Analysis
Third paragraph
First bullet, first sentence previously read:

On Study Day 1 and the Week 4 visit, subjects will have their dose administered by study site personnel with food.

Has been changed to read:

On Study Day 1 and the Week 4 visit, subjects will have their dose administered by study site personnel after food.

Section 5.3.7 Pharmacogenetic Variables
Last paragraph previously read:

DNA samples from subjects who separately consent for additional pharmacogenetic analysis may be sequenced and data analyzed for genetic factors possibly contributing to the disease or to the subject's response to study treatment, in terms of pharmacokinetics, pharmacodynamics, 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 (including IL28B). Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. Pharmacogenetic analyses will be limited to studying response to HCV therapy; no other analyses will be performed.

Has been changed to read:

DNA samples from subjects who separately consent for additional pharmacogenetic analysis may be sequenced and data analyzed for genetic factors possibly contributing 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 the disease or drug response (including IL28B). Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. Pharmacogenetic analyses will be limited to studying response to the HCV therapy; no other analyses will be performed.

Section 5.5.3 Method of Assigning Subjects to Treatment Groups
Third paragraph previously read:

The randomization will be stratified by prior IFN-experience (naïve versus experienced) and baseline HCV RNA (< or ≥ 6 million IU/mL).

Has been changed to read:

The randomization will be stratified by prior IFN-experience (naïve versus experienced) and Screening HCV RNA (< or ≥ 6 million IU/mL).

Section 6.1.5 Adverse Event Reporting
"Primary TA MD:"
"Title" previously read:

Assistant Medical Director

Has been changed to read:

Japan Project Head/Associate Medical Director

Section 6.1.7.5 Management of Increases in ALT
First paragraph previously read:

If a subject experiences a post-baseline increase in ALT to > 5 × ULN and 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:

Has been changed to read:

If a subject experiences a post-baseline increase in ALT to ≥ 5 × ULN and 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:

Section 7.0 Protocol Deviations
"Alternate Contact:" previously read:

Alternate Contact:

Has been changed to read:

Alternate Contact:

Section 8.1.2.2 Secondary Efficacy Endpoints
Last paragraph previously read:

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

Has been changed to read:

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

Section 8.3 Randomization Methods
Previously read:

Approximately 120 subjects meeting all eligibility criteria will be randomized in a 2:1 ratio into Arms A and B and randomization will be stratified by prior IFN-experience (naive versus experienced) and baseline HCV RNA (< or ≥ 6 million IU/mL).

Has been changed to read:

Approximately 120 subjects meeting all eligibility criteria will be randomized in a 2:1 ratio into Arms A and B and randomization will be stratified by prior IFN-experience (naive versus experienced) and Screening HCV RNA (< or ≥ 6 million IU/mL).

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Clinical
		CMC Group
		Clinical
		Pharmacokinetics
		Clinical
		Clinical
		Statistics
		Bioanalysis

Has been changed to read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		CMC Group
		Clinical
		Pharmacokinetics
		Clinical
		Clinical
		Statistics
		Bioanalysis

Document Approval

Study M15828 - A Randomized, Open-Label, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults with Genotype 2 Chronic Hepatitis C Virus Infection (CERTAIN-2) - Amendment 2 - 17Jun2016

Version: 1.0 **Date:** 20-Jun-2016 02:45:39 PM **Company ID:** 06202016-00F9F68129986C-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	17-Jun-2016 03:05:26 PM	Approver
	17-Jun-2016 04:33:27 PM	Approver
	17-Jun-2016 05:58:36 PM	Approver
	17-Jun-2016 07:06:51 PM	Approver
	18-Jun-2016 07:27:30 AM	Approver
	18-Jun-2016 01:59:14 PM	Author
	18-Jun-2016 02:36:36 PM	Approver
	18-Jun-2016 11:19:03 PM	Approver
	20-Jun-2016 02:45:37 PM	Approver