1.0 Title Page

Clinical Study Protocol M15-942

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

(MAGELLAN-3)

Incorporating Administrative Change 1 and Amendments 1 and 2

AbbVie Investigational Product:	ABT-493/ABT-530
Date:	06 November 2017
Development Phase:	3b
Study Design:	This is an open-label, multicenter study.
EudraCT Number:	2016-002491-26
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie)*
Sponsor/Emergency Contact:	Therapeutic Area Scientific [redacted] 1 North Waukegan Road North Chicago, IL 60064 Office: Mobile: [redacted] eFax: Therapeutic Area Medical [redacted] 1 North Waukegan Road North Chicago, IL 60064 Office: Mobile: [redacted] eFax: Emergency 24 hour Number: +1 973-784-6402

* 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	15 July 2016
Amendment 1	31 August 2016
Administrative Change 1	09 February 2017

The purpose of this amendment is to:

- Update Section 1.0, Title Page, and Section 6.1.5, Adverse Event Reporting

  Rationale: *A 24-hour emergency number was added in the event emergency calls need to be re-directed to a designated backup AbbVie Therapeutic Area Medical Director (TA MD). Language was updated, per the latest AbbVie protocol template.*
- Update Section 1.2 Synopsis and Section 1.3 List of Abbreviations and Definitions of Terms, and Appendix C, Study Activities – Treatment Period

  Rationale: *Updated to be consistent with other updates made throughout the protocol.*
- Update Section 3.0, Introduction

  Rationale: *Updated the section to reflect the recent approval of glecaprevir/pibrentasvir in some parts of the world and the number of patients that were enrolled in the registrational or Phase 2b studies.*
- Update Table 1, In Vitro Antiviral Activity of ABT-493 and Other Protease Inhibitors Against HCV Genotypes 1, 2, 3, 4, and 6, Section 3.0, Introduction, Section 14.0, Investigator's Agreement, and Section 15.0, Reference List.

  Rationale: *Updated in-text citations, table, and text to refer to the updated Glecaprevir/Pibrentasvir Fixed-Dose Combination Investigator's Brochure.*
- Update Section 4.0, Study Objective, Figure 1, Study Schematic (Treatment Period), Section 5.2, Selection of Study Population, Section 5.2.1, Inclusion Criteria, Section 5.2.2, Exclusion Criteria, and Section 6.1.7.4, Management of Decreases in Hemoglobin for Subjects Receiving RBV.

Rationale: *Updated study design and several entry criteria to broaden the study population in order to receive virologic failures from AbbVie's Phase 3b/4 glecaprevir/pibrentasvir studies.*

- Update Section 5.1, Overall Study Design and Plan: Description, Table 7, Treatment Arm Allocation in Study M15-942, and Section 8.2, Determination of Sample Size.

  Rationale: *Updated the study's sample size and the distribution of subjects in each treatment arm to allow for subjects experiencing virologic failure in AbbVie's Phase 3b/4 glecaprevir/pibrentasvir studies to also be enrolled in Study M15-942.*

- Update Section 5.1, Overall Study Design and Plan: Description, Section 5.5.4, Selection and Timing of Dose for Each Subject, and Table 8, Ribavirin Dosing Recommendations

  Rationale: *Updated the section and added a table to include RBV dosing recommendations for adolescent subjects based on their baseline age and weight.*

- Update Section 5.1, Overall Study Design and Plan: Description, Table 7.

  Rationale: *Added a footnote to clarify in which arm subjects with mixed and unknown HCV genotypes will be enrolled in.*

- Update Section 5.1.1, Screening, Section 5.3.1.1, Study Procedures, Section 5.3.2.1, Collection of Samples for Analysis, Section 5.3.2.2, Handling/Processing of Samples, Section 5.3.2.3, Disposition of Samples, Section 5.3.2.4, Measurement Methods, and Appendix C, Study Activities – Treatment Period

  Rationale: *Updated the sections to remove collection of dosing information for HIV ARV and collection/analysis of HIV ARV PK samples because sufficient data regarding the PK of these agents when co-administered with glecaprevir/pibrentasvir is now available.*

- Update Section 5.1.1.1, Rescreening, Section 5.6.4.2, Rationale for Duration Selections, Section 8.1, Statistical and Analytical Plans, and Section 8.1.2.3 Sensitivity Analysis

  Rationale: *Given the demonstrated pan-genotypic activity of the glecaprevir/pibrentasvir combination, subjects infected with more than*

one HCV genotype are being allowed. Statistical analyses have been updated to include these subjects. Section was also updated to be consistent with other sections of the protocol.

- Update Section 5.2.1, Inclusion Criteria, Section 5.2.2, Exclusion Criteria, Section 5.2.4, Contraception Recommendations, Section 5.3.1, Study Procedures, Section 6.1.6, Pregnancy, and Appendix C, Study Activities – Post-Treatment (PT) Period

  Rationale: *Updated the sections to clarify that the more restrictive approach to contraception between the local RBV label and the protocol language should be used.*

- Update Section 5.2.2, Exclusion Criteria, Section 6.1.8, Collection of Data Regarding Known AIDS-Defining Conditions, and Appendix D, List of AIDS-Defining Conditions
- ***Rationale:*** *Updated the abbreviation for AIDS-Defining Conditions throughout the protocol and the list of AIDS-Defining Conditions.*
- Update Section 5.2.2, Exclusion Criteria, Criterion 20.

  Rationale: *Added a new exclusion criterion to clarify that subjects who have documented HCV reinfection after receiving glecaprevir/pibrentasvir in the parent AbbVie study are not eligible for this study, since they are essentially treatment-naïve for the new infection.*

- Update Section 5.2.3, Prior and Concomitant Therapy.

  Rationale: *Updated guidance for medications taken during the treatment and post-treatment period.*

- Update Section 5.2.3.4, Prohibited Therapy, Table 9, Medications and Supplements Prohibited with ABT-493/ABT-530 Administration.

  Rationale: *Updated the section text and Table 9 footnote to require the investigator to discontinue any medications or supplements based on the most recent drug interaction data. Guidance for investigators for prohibited medications or supplements administered with ABT-493/ABT-530 was also provided. Ethinyl estradiol was added to the table. Added progestogen in the section to be consistent with the language in the AbbVie protocol template.*

- Update Section 5.3.1.1, Study Procedures, Hepatocellular Carcinoma Screening: Liver Ultrasound.

  Rationale: *Updated language to ensure all cirrhotic subjects will have a protocol required liver ultrasound result for the last post-treatment visit, in order to determine more accurately if the subject was HCC-free during the course of the observation period.*

- Update Section 5.3.2.1, Collection of Samples for Analysis.

  Rationale: *To clarify pharmacokinetic samples are not to be collected on Day 1 and dosing on Week 4 is not required to occur at the site.*

- Update Section 5.4.1.1, HCV Virologic Failure Criteria.

  Rationale: *The section was re-written to clarify the HCV virologic failure criteria and that cases of confirmed HCV reinfection, for which a definition was provided, are excluded from the definition of relapse.*

- Update Section 5.5.1, Treatments Administered.

  Rationale: *Updated the section for clarity and to rectify when dosing is to be administered at site. In addition, text was added to guide the exceptional use of commercial supplies in the study.*

- Update Section 5.6.4.1, Rationale for Dose Selections.

  Rationale: *Deleted the fourth paragraph as the information is not relevant to this protocol.*

- Update Section 5.2.4, Contraception Recommendations, Section 6.0, Complaints, Section 6.1.3, Relationship to Study Drug, Section 6.1.5, Adverse Event Reporting, Section 6.2.2, Reporting, Section 7.0, Protocol Deviations, Section 9.1, Independent Ethics Committee (IEC) or Institutional Review Board (IRB), Section 9.3, Subject Information and Consent, Section 10.1, Source Documents, and Section 13.0, Completion of the Study

  Rationale: *Language was updated, per the latest AbbVie protocol template.*

- Update Section 6.1.7.5, Management of Increases in ALT.

  Rationale: *Updates were made to specify the minimum requirements for laboratory assessment of ALT elevations and the criteria for study drug discontinuation. Updated the section by deleting anti-hepatitis A virus*

immunoglobulin test and replacing it with anti-hepatitis A virus total test as a result of an error in the original list of tests.

- Update Section 8.1, Statistical and Analytical Plans.

  Rationale: *To specify that an interim analysis may be conducted as part of regulatory authority interactions.*

- Update Section 8.1.2.1, Primary Efficacy Endpoints.

  Rationale: *The text was updated to comply with Regulatory Authority feedback, which requested that, for high SVR12 rates that are less than 100%, the Wilson score test be used for calculating the 95% confidence interval in the primary efficacy analysis, rather than using the normal approximation to the binomial distribution.*

- Update Appendix B, List of Protocol Signatories

  Rationale: *Updated to reflect changes in signatories.*

- Update Appendix C, Study Activities.

  Rationale: *Updated the tables and footnotes to be consistent with the changes made in the body of the protocol text.*

- Incorporated Protocol Administrative Change 1.

  Rationale: *In accordance with AbbVie's protocol preparation procedures.*

- Minor clerical updates/typographical correction made throughout the protocol.

  Rationale: *Revised text to correct typographical errors, improve consistency and readability throughout the protocol.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-942
Name of Study Drug: ABT-493/ABT-530, sofosbuvir (SOF), ribavirin (RBV)	**Phase of Development:** 3b
Name of Active Ingredient: ABT-493/ABT-530, SOF, RBV	**Date of Protocol Synopsis:** 06 November 2017
Protocol Title: An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Combination with Sofosbuvir and Ribavirin in Chronic Hepatitis C (HCV) Infected Subjects Who Have Experienced Virologic Failure in AbbVie HCV Clinical Studies (MAGELLAN-3)	
Objectives: • The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving a 12-week post-treatment sustained virologic failure response (SVR_{12}) in each treatment arm and safety of ABT-493/ABT-530 plus SOF and RBV in adults or adolescents with chronic HCV GT1-6 infection who previously failed HCV treatment in an AbbVie HCV clinical study, designated as an AbbVie HCV parent study. • Secondary objectives are to assess the percentage of subjects with HCV on-treatment virologic failure, and the percentage of subjects with HCV virologic relapse.	
Investigators: Multicenter; investigator information on file at AbbVie	
Study Sites: Approximately 40 sites who participated in an AbbVie HCV parent study.	
Study Population: Subjects who have experienced virologic failure after receiving regimens containing ABT-493/ABT-530 in an AbbVie HCV parent study. Subjects who have experienced virologic failure during or after receiving ombitasvir/paritaprevir/r + dasabuvir (3D), ombitasvir/paritaprevir/r (2D) in an AbbVie HCV parent study may be enrolled at AbbVie's discretion.	
Number of Subjects to be Enrolled: Approximately 50 subjects.	

Methodology:

This is a Phase 3b, open-label, non-randomized, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in combination with SOF and RBV in HCV GT1 – 6-infected subjects including subjects with compensated cirrhosis and/or HIV-1 coinfection who have experienced virologic failure while participating in an AbbVie HCV parent study. Approximately 50 subjects will be enrolled. Treatment arm allocation will be based on HCV genotype, cirrhosis status, and treatment experience with protease inhibitor (PI) and/or NS5A inhibitor (NS5Ai)-containing regimens prior to enrolling in the AbbVie HCV parent study.

Treatment Arm Allocation in Study M15-942

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

* NC = non-cirrhotic; C = cirrhotic

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

- Arm A: Subjects will receive orally ABT-493/ABT-530 300/120 mg QD, SOF 400 mg QD, RBV 600 mg to 1200 mg daily in two divided doses (based on baseline age and weight) for 12 weeks
- Arm B: Subjects will receive orally ABT-493/ABT-530 300/120 mg QD, SOF 400 mg QD, RBV 600 mg to 1200 mg daily in two divided doses (based on baseline age and weight) for 16 weeks

Arm A will enroll approximately 5 subjects, and Arm B will enroll approximately 45 subjects. All subjects administered at least one dose of study drugs will be followed for 24 weeks in the Post-Treatment Period to monitor HCV RNA and to evaluate efficacy and the emergence and/or persistence of resistance-associated viral variants.

Planned visits in the Treatment Period consist of Day 1, Weeks 2, 4, 8, and 12 for all subjects and an additional Week 16 visit for subjects in Arm B. During the Post-Treatment Period, subjects will have visits at Post-Treatment Weeks 4, 12, and 24. Efficacy and safety data will be monitored throughout the study. As this is an open-label study, safety will be reviewed by AbbVie.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female subjects must be adults (18 years of age or older) or adolescents (12 to less than 18 years of age weighing at least 35 kg).
2. Subject must have experienced virologic failure during or after treatment with ABT-493/ABT-530 in an AbbVie HCV parent study. Subjects who have experienced virologic failure during or after receiving ombitasvir/paritaprevir/r + dasabuvir (3D), or ombitasvir/paritaprevir/r (2D) in an AbbVie HCV parent study may be enrolled at AbbVie's discretion. Treatment in the parent study must have been completed or discontinued at least 1 month prior to the Screening Visit.
3. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
4. Cirrhotic Subjects must have compensated cirrhosis, (Child-Pugh score of ≤ 6) at Screening and no current or past evidence of Child-Pugh B or C Classification or no clinical history of liver decompensation, including ascites noted on physical exam, hepatic encephalopathy or esophageal variceal bleeding.
5. Cirrhotic Subjects must have absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound (US), computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative US at Screening.

Main Exclusion:

1. History of severe, life-threatening or other clinically significant sensitivity to any study drug or drug component.
2. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for 4 months after the last dose of study drug, or as directed per the local RBV label, whichever is more restrictive.
3. 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, and failure in an AbbVie HCV parent study due to non-virologic reasons.
4. Positive test result at Screening for hepatitis B surface antigen (HBsAg).
5. Screening laboratory analyses showing calculated creatinine clearance < 30 mL/min.
6. Discontinuation from the AbbVie HCV parent study for reasons other than virologic failure (e.g., non-adherence, lost to follow-up, and/or the occurrence of an adverse event).
7. Receipt of any HCV treatment after failing the treatment regimen in the AbbVie HCV parent study.

Investigational Products:	ABT-493/ABT-530 mg 100 mg/40 mg Film-coated Tablet Sofosbuvir 400 mg Film-coated Tablet Ribavirin 200 mg Film-coated Tablet
Doses:	ABT-493/ABT-530: 300 mg/120 mg QD (3 tablets) Sofosbuvir: 400 mg QD (1 tablet) Ribavirin: • For subjects aged 18 or more: 1000 mg or 1200 mg daily in two divided doses • For subjects 12 less than 18 years old: 600 mg to 1200 mg daily in two divided doses
Mode of Administration:	Oral with food
Reference Therapy:	N/A
Dose:	N/A
Mode of Administration:	N/A
Duration of Treatment: 12 or 16 weeks.	

Criteria for Evaluation:

Efficacy:

Efficacy will be assessed utilizing plasma HCV RNA levels throughout the study.

Resistance:

The following information will be tabulated and summarized: 1) for all subjects receiving study drug 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 who do not achieve SVR_{12} and who have a post-baseline sample, all treatment-emergent variants relative to baseline.

Pharmacokinetic:

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

Safety:

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

Statistical Methods:

Efficacy:

The primary efficacy endpoint is the percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm and overall. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of virologic failures is less than 5, then the Wilson's score method will be used for the confidence interval instead.

The secondary efficacy variables are:

- The percentage of subjects with on-treatment HCV virologic failure in each treatment arm and overall;
- The percentage of subjects with post-treatment HCV virologic relapse in each treatment arm and overall.

The number and percentage of subjects meeting each secondary efficacy endpoint will be summarized along with a two-sided 95% confidence interval using the Wilson score method. Analyses of additional efficacy endpoints and efficacy subgroup analyses will be performed.

Resistance:

For all subjects receiving study drugs and with available samples, the variants at signature resistance-associated amino acid positions at baseline identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drugs 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 NGS and comparison to the baseline sequence, 2) the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral variants by NGS.

Pharmacokinetic:

Plasma concentrations of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), and RBV will be tabulated for each subject and treatment arm. Summary statistics will be computed for each treatment arm.

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). Safety summaries will be provided by treatment arm and overall. 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 MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug. Change from baseline in laboratory tests and vital signs measurements to each time point of collection will be summarized, and values that are potentially clinically significant, according to predefined criteria, will be summarized by treatment arm and overall.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

2D	Paritaprevir/ritonavir/ombitasvir
3D	Paritaprevir/ritonavir/ombitasvir + dasabuvir
3TC	Lamivudine
Ab	Antibody
ABC	Abacavir
ABT-450	Paritaprevir
ADC	AIDS-Defining Conditions
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APRI	Aminotransferase/platelet ratio index
aPTT	Activated partial thromboplastin time
ART	Antiretroviral Treatment
AST	Aspartate aminotransferase
BID	Twice Daily
BMI	Body Mass Index
BOC	Boceprevir
BUN	Blood urea nitrogen
CBP	Childbearing potential
COBI	Cobicistat
CrCl	Creatinine clearance
CRF	Case report form
CT	Computed Tomography
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DCV	Daclatasvir
DNA	Deoxyribonucleic acid
DRV	Darunavir
DSV	Dasabuvir
DTG	Dolutegravir
EC	Ethics Committee

ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EU	European Union
EVG	Elvitegravir
FDV	Faldaprevir
FSH	Follicle stimulating hormone
FTC	Emtricitabine
GAM	Generalized additive method
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
Hemoglobin A1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HIV-2	Human immunodeficiency virus type 2
HIV Ab	Human immunodeficiency virus antibody
HCC	Hepatocellular carcinoma
ICH	International Council on Harmonisation
IEC	Independent ethics committee
IFN	Interferon
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International units
IUD	Intrauterine device
LDV	Ledipasvir
LLOD	Lower limit of detection

LLOQ	Lower limit of quantification
LPV	Lopinavir
LPV/r	Lopinavir and ritonavir
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NGS	Next generation sequencing
NS3A	Nonstructural viral protein 3A
NS4A	Nonstructural viral protein 4A
NS5A(i)	Nonstructural viral protein 5A (inhibitor)
NS5B(i)	Nonstructural viral protein 5B (inhibitor)
OTVF	On-treatment Virologic Failure
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PegIFN/RBV	Combination of pegylated-interferon alfa-2a or alfa-2b and ribavirin
PI	Protease Inhibitor
POR	Proof of Receipt
PR	pegInterferon and ribavirin
PT	Post-Treatment/preferred term
QD	Once daily
RAL	Raltegravir
RBC	Red blood cells
RBV	Ribavirin
RDV	Ravidasvir
RNA	Ribonucleic acid
RPV	Rilpivirine
RTV or r	Ritonavir
SAE	Serious adverse event
SAM	S-adenosyl-L-methionine
SD	Standard Deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMV	Simeprevir
SOF	Sofosbuvir
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response

SVR_4	Sustained virologic response 4 weeks post dosing
SVR_{12}	Sustained virologic response 12 weeks post dosing
SVR_{24}	Sustained virologic response 24 weeks post dosing
TAF	Tenofovir alafenamide
TA MD	Therapeutic Area Medical Director
TA SD	Therapeutic Area Scientific Director
TDF	Tenofovir disoproxil fumarate
TVR	Telaprevir
ULN	Upper limit of normal
US	Ultrasound
WBC	White blood cells

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the plasma concentration-time curve
AUC_{0-24}	AUC for the 24-hour dosing interval
CL/F	Apparent oral plasma clearance
C_{max}	Maximum observed plasma concentration
NONMEM	Non-linear mixed-effect modeling
PK	Pharmacokinetic
T_{max}	Time to maximum observed plasma concentration (C_{max})
V/F	Apparent Volume of distribution

Definition of Terms

Study Drug	ABT-493, ABT-530, Sofosbuvir and Ribavirin
Study Day 1	First day of study drug dosing
AbbVie HCV Parent Study	The most recent AbbVie study in which a subject experienced virologic failure prior to entering Study M15-942
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 virus (HCV) infection is a global health problem, with over 170 million individuals infected worldwide.[1] There are six major HCV genotypes (GT), GT1 to GT6, and each genotype expresses a distinct epidemiological pattern across the world. Patients with chronic HCV infection are at high risk of developing cirrhosis, death related to the complications of cirrhosis, and developing hepatocellular carcinoma.[2] Successful treatment of HCV was shown to significantly reduce the risk of disease progression and related mortality as well as the development of hepatocellular carcinoma.[3,4]

Currently approved IFN-free and, in some cases, RBV-free DAA combination regimens, such as sofosbuvir (SOF)/ledipasvir (LDV), ombitasvir/paritaprevir/ritonavir with (3D) or without (2D) dasabuvir, SOF and daclatasvir (DCV), and elbasvir/grazoprevir represent substantial progress in the treatment of HCV infection. These regimens are associated with significant improvement of the sustained virologic response (SVR) rate and safety profile in the approved patient populations. However, these IFN-free regimens are not equally potent across all HCV genotypes and subtypes, and across all subpopulations. They may require co-administration with RBV in some sub-populations.

The next generation DAA regimens have high potencies across all HCV genotypes and across patient subpopulations, including Abbvie's ABT-493/ABT-530 or glecaprevir/pibrentasvir (GLE/PIB). GLE/PIB is approved in some parts of the world, including Europe and the United States, under the brand name MAVIRET® or MAVYRET™, respectively.

ABT-493 (NS3/4A protease inhibitor [PI]) and ABT-530 (NS5A inhibitor [NS5Ai]) are denoted as next generation compounds because they each demonstrated potent pan-genotypic antiviral activity against all major HCV genotypes, i.e., GT1 through GT6 and they are potent against known common single resistance-associated amino acid variants with no or little loss of potency.

ABT-493

ABT-493 is an NS3/4A protease inhibitor (PI) with potent, pangenotypic activity and a high barrier to resistance with activity against common variants that emerge following exposure to first generation PIs. AbbVie is developing ABT-493 to be used in combination with the NS5A inhibitor ABT-530 for the treatment of chronic HCV infection. ABT-493 is highly active against replicons containing wild-type HCV NS3 from GT1, 2, 3, 4, and 6. ABT-493 activity against GT5 NS3 is unknown because a replicon with GT5 NS3 is not currently available (Table 1). Based on findings that each of 5 well characterized HCV PIs, including 2 linear and 3 macrocyclic PIs, demonstrated similar activity against GT2a, 5a, and 6a NS3 protease,[5] it is predicted ABT-493 would inhibit NS3 protease of GT5a with activity similar to that of GT2a and 6a.

Table 1. In Vitro Antiviral Activity of ABT-493 and Other Protease Inhibitors Against HCV Genotypes 1, 2, 3, 4, and 6

	Stable HCV Replicon EC_{50} (nM)					
Protease Inhibitor	**GT1a**	**GT1b**	**GT2a**	**GT3a**	**GT4a**	**GT6a**
ABT-493	0.85	0.94	2.2[a]	1.9	2.8	0.86
Paritaprevir[1]	1.0	0.21	5.3[a]	19	0.09	0.68
Simeprevir[2,3]	13	9.4	15	472	NA	NA
Asunaprevir[4]	4.0	1.2	230	1162	NA	NA
Grazoprevir	0.38	0.87	1.3	36	1.2	0.89
GS-9451[5]	13	5.4	316	NA	NA	NA
GS-9857[6]	3.9	3.3	3.7	6.1	2.9	1.5

NA = not available

a. Study conducted at Southern Research Institute.

1. AbbVie. Dasabuvir, Ombitasvir, Paritaprevir, Ritonavir Investigator's Brochure Edition 1. 2016.[6]
2. Simeprevir prescribing information.[7]
3. Chase R, et al. IAPAC, 2013.[8]
4. McPhee F, et al. AAC, 2012.[9]
5. Yang H, et al. AAC, 2014.[10]
6. Taylor J, et al. EASL, 2015.[11]

ABT-493 retains activity against common GT1 NS3 single-position resistance-associated variants in comparison with other PIs as described in Table 2.

Table 2. Anti-Viral Activity of ABT-493 and Other PIs Against Common HCV GT1 NS3 Single-Position Variants

	HCV Transient Replicon EC_{50} (nM)						
	GT1a				GT1b		
Inhibitor	**Wild Type**	**R155K**	**D168A**	**D168V**	**Wild Type**	**R155K**	**D168V**
ABT-493	0.28	0.16	0.84	0.93	0.54	0.32	1.3
Paritaprevir	1.4	51	70	135	0.11	4.4	17
Grazoprevir	0.3	0.9	29	11	0.4	0.5	5.9
Simeprevir	4.0	172	100	3120	11	260	17,920
Asunaprevir	0.76	16	17	283	0.86	23	241

References: Chase R et al,[8] Lenz O et al,[12] McPhee F et al[9]

The pharmacokinetics of ABT-493 has been evaluated at doses up to 1200 mg QD. ABT-493 reached T_{max} around 3 to 4 hours with an elimination half-life of 6 to 9 hours. ABT-493 exposures increased in a greater than dose proportional manner across the 25 mg to 1200 mg dose range. Orally administered ABT-493 was predominantly cleared through the biliary-fecal route. The percentages of the ABT-493 dose recovered in urine were less than 4%. No metabolite was identified in systemic circulation.

In summary, ABT-493 is a potent, pangenotypic PI with high potential for treatment of chronic HCV infection. A detailed discussion of the preclinical toxicology, metabolism, and pharmacology and Phase I data can be found in the Investigator's Brochure.[13]

ABT-530

ABT-530 is an NS5A inhibitor (NS5Ai) with potent, pangenotypic activity and a high barrier to resistance with activity against common variants that emerge following exposure to first generation NS5Ai. ABT-530 is highly active against HCV replicons containing wild-type HCV NS5A from GT1, 2, 3, 4, 5, and 6 (Table 3).

Table 3. In vitro Antiviral Activity of ABT-530 and Other NS5A Inhibitors Against HCV Genotypes 1 through 6.

	Stable HCV Replicon EC_{50} (pM)							
NS5A Inhibitor	**GT1a**	**GT1b**	**GT2a**	**GT2b**	**GT3a**	**GT4a**	**GT5a**	**GT6a**
ABT-530	2	4	2[a]	2	2	2	1	3
Ombitasvir	14	5	12	4	19	2	3	366
Daclatasvir	22	3	13,000	NA	530	13	5	74
Ledipasvir	31	4	21,000	16,000	168,000	390	150	1100
Velpatasvir	12	15	9	8	12	9	75	6
Elbasvir	4	3	3	3000	20	3	1	3
MK-8408	1	2	1	4	2	2	1	4

NA = not available

a. Study conducted at Southern Research Institute.

References: Wang C, et al. AAC, 2014;[14] Cheng G, et al. EASL, 2012;[15] Harvoni prescribing information;[16] Cheng G, et al. EASL, 2013;[17] Liu R, et al. EASL, 2012;[18] Asante-Appiah E, AASLD, 2014[19]

ABT-530 retains activity against common single resistance-associated amino acid variants in NS5A (Table 4). ABT-530 is > 100-fold more active than the first generation NS5Ai (ombitasvir, daclatasvir, and ledipasvir) against key resistance-associated variants selected by these inhibitors in the clinic at GT1 NS5A amino acid positions 28, 30, 31, and 93. Its genetic barrier to resistance is higher than that of ombitasvir across all GTs.

Table 4. Anti-Viral Activity of ABT-530 and Other NS5A Inhibitors Against Common HCV GT1 NS5A Single-Position Variants

	HCV Replicon EC_{50} (pM)							
	GT1a					GT1b		
Inhibitor	**Wild Type**	**M28T**	**Q30R**	**L31M**	**Y93H**	**Wild Type**	**Y93H**	**Y93N**
ABT-530	0.72	1.5	1.2	0.76	4.8	2.2	1.4	1.0
Ombitasvir	2.7	24,500	2180	4.8	> 100,000	0.79	60	167
Daclatasvir	6.0	4050	7300	2020	32,200	2.5	62	74
Ledipasvir	51	1801	12,420	14,610	86,430	4.0	5200	NA

References: Fridell RA et al,[20] Wong KA et al[21]

The pharmacokinetics of ABT-530 has been evaluated at doses up to 600 mg QD. ABT-530 reached a T_{max} around 3 to 5 hours, with an elimination half-life of 12 to 17 hours. ABT-530 exposures increased in a greater than dose-proportional manner across the 1.5 mg to 120 mg dose range and approximately dose proportionally from the 120 mg to 600 mg single doses. ABT-530 undergoes minimum renal elimination. Orally administered ABT-530 was predominantly cleared through the biliary-fecal route as unchanged parent drug.

In summary, ABT-530 is a potent, pangenotypic NS5Ai with high potential for treatment of chronic HCV infection. A detailed discussion of the preclinical toxicology, metabolism, and pharmacology and Phase 1 data can be found in the Investigator's Brochure.[13]

ABT-493 and ABT-530

When ABT-493 was given in combination with ABT-530 in healthy volunteers, preliminary results showed ABT-493 exposures were not significantly changed when co-administered with ABT-530 (≤ 31% difference); however, the exposure of ABT-530 increased in an ABT-493-dose-dependent manner (from 1.5-fold at 100 mg ABT-493 up to 3- to 4-fold at 400 mg ABT-493).

Results of clinical DDI studies conducted to date have shown that as perpetrators of DDIs, ABT-493/ABT-530 combination had no clinically meaningful impact on drugs that are substrates of CYP or UGT enzymes. The ABT-493/ABT-530 combination increased exposure of substrates for P-gp, BCRP, OATP1B1, and OATP1B3 transporters.

Except for some OATP inhibitors (e.g., high dose cyclosporine), ritonavir-boosted protease inhibitors and P-gp inducers, ABT-493 and ABT-530 exposures were minimally affected by co-administrations of other drugs. ABT-493 is a substrate of OATP and inhibition of OATP increases ABT-493 exposure. When ABT-493 + ABT-530 was administered with cyclosporine (400 mg), an OATP inhibitor, ABT-493 exposure was up to 5.1-fold of DAAs alone. The increased exposures observed were not associated with

clinically significant safety findings. Protease inhibitors, as a class, have potential to inhibit OATP, thus larger exposure increases in ABT-493 with ritonavir boosted protease inhibitors than with ritonavir alone may result from interaction of ABT-493 with both the protease inhibitor and ritonavir components.

ABT-493/ABT-530 possesses greater antiviral activity as compared to the ombitasvir/paritaprevir/ritonavir + dasabuvir regimen, while also maintaining adequate activity against variants that confer resistance to ombitasvir and paritaprevir.[22-24]

For a more detailed discussion of drug-drug interaction studies please refer to the Investigator's Brochure.[13]

HCV/HIV-1 Co-Infection

HCV and HIV-1 co-infection is associated with accelerated hepatic fibrosis progression and higher rates of liver decompensation and death compared to HCV monoinfection, and liver disease is a leading cause of non-AIDS-related mortality among HIV-1-infected patients.[25-27] Treatment of HIV-1 with antiretroviral therapy and treatment of HCV have independently been shown to delay the progression of fibrosis and reduce complications from end-stage liver disease among co-infected patients.[28,29]

According to data from different trials, the effectiveness of DAA-based therapy appears to be similar between HCV mono-infected individuals and HCV/HIV-1 co-infected individuals, as shown in Table 5.[30] Per the most recent AASLD treatment guidelines, it is recommended that HCV/HIV-1 co-infected patients be treated and re-treated the same as HCV mono-infected patients, albeit with attention paid to potential drug-drug interactions with anti-retroviral medications.[31]

Table 5. SVR Rates Observed in HCV-Mono-Infected and HCV/HIV-1 Co-Infected Patients Treated with All-Oral HCV DAA Regimens

Study	Regimen, Duration, Population Studied	ITT SVR_{12} Rate in HCV/HIV-1 Co-Infected Population	ITT SVR_{12} Rate in Similar HCV Mono-Infected Population (Study or Studies)
TURQUOISE-I[32]	Ombitasvir/Paritaprevir/ritonavir + Dasabuvir + RBV, 12 weeks, GT1 HCV/HIV-1 Co-infection	94%	92% – 96% (SAPPHIRE-I and –II, TURQUOISE-II)[33-35]
ION-4[36]	Sofosbuvir/Ledipasvir, 12 weeks, GT1, 4 HCV/HIV-1 Coinfection	96%	93% – 99% (ION-1, -2 and -3)[37-39]
ALLY-2[40]	Sofosbuvir + Daclatasvir, 12 weeks, GT1 – 4 HCV/HIV-1 Coinfection	97%	95% (A1444040)[41]
C-EDGE CO-INFECTION[42]	Grazoprevir/Elbasvir, 12 weeks, GT1, 4, 6 HCV/HIV-1 Coinfection	96%	91% – 97% (C-EDGE TN, C-EDGE TE, C-WORTHY)[43,44]

ARV Drug-Drug Interaction Studies with ABT-493 and ABT-530

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

The ABT-493 + ABT-530 combination had no clinically meaningful impact on the exposures (≤ 80%) of evaluated ARV regimens: ritonavir-boosted protease inhibitors (darunavir, lopinavir), rilpivirine, raltegravir, emtricitabine and tenofovir disoproxil fumarate (TDF). ABT-493 and ABT-530 exposures were not affected by rilpivirine and raltegravir.

Dolutegravir, lamivudine and abacavir (Triumeq®) coadministered with ABT-493 + ABT-530 has recently been evaluated in a DDI Study M15-584. Coadministration was safe and well tolerated with mild side effects reported. ABT-493 and ABT-530 had no impact on dolutegravir, lamivudine and abacavir exposures. There was a mild decrease in ABT-493 and ABT-530 exposures of no clinical significance.

Efavirenz induces P-gp and exposures of ABT-493 and ABT-530 in the presence of efavirenz were approximately 3- and 2-fold lower, respectively, and thus will not be allowed in this study.

When ABT-493 was administered with ritonavir, exposure of ABT-493 was 2-fold of ABT-493 exposure alone. Coadministration of ABT-493 + ABT-530 with ritonavir boosted protease inhibitors, darunavir QD or lopinavir BID resulted in further increases in ABT-493 exposure of 3- to < 5-fold and < 2 fold exposure to ABT-530 without change in the LPV or DRV exposures. In spite of the increase in ABT-493 exposures while coadministered with DRV/r or LPV/r, it was well tolerated, with mild side effects. Coadministration of ABT-493 + ABT-530 with ritonavir boosted atazanavir was studied in a DDI study that was terminated early due to an increase in ABT-493 exposure up to 16-fold and ABT-530 exposure up to 3-fold with Grade 1 and 2 increases in alanine aminotransferase (ALT) and Grade 2 to 3 increase in total bilirubin (predominately indirect).

Study M15-584 evaluated the drug interaction profile when ABT-493/ABT-530 300 mg/120 mg is co-administered with Genvoya® (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir alafenamide10 mg QD). Co-administration was safe and well tolerated, with mild side effects reported and one grade 3 neutropenia deemed related to the combination of Genvoya, ABT-493 and ABT-530 in a black male subject with baseline low absolute neutrophil count (ANC), leading to premature study drug discontinuation. The ABT-493 exposure increased 3-fold and the ABT-530 exposure increased 57%, with non-clinically significant increase in elvitegravir and cobicistat exposures. Thus, cobicistat boosted elvitegravir will be allowed in this study.

In addition, ritonavir and cobicistat-boosted HIV-1 protease inhibitors (darunavir and lopinavir) will be allowed in the non-cirrhotic arm only. These HIV-1 protease inhibitors will not be allowed in cirrhotic subjects, as the ABT-493 predicted exposures in this population approach the ALT 5% Grade 2 threshold.

For a more detailed discussion of drug-drug interaction studies please refer to the Investigator's Brochure.[13]

Clinical Study Results

Studies M14-867 and M14-868 (data on file)[13] are Phase 2 studies designed to assess the efficacy and safety of the combination of ABT-493 and ABT-530 in cirrhotic and non-cirrhotic subjects with HCV GT1 – 6 infection following 8 or 12 weeks of administration. In these two studies, high SVR rates have been achieved for the combination of ABT-493 and ABT-530 at the dose strength consistent with the Phase 3 doses, i.e., ABT-493 300 mg and ABT-530 120 mg (Table 6). In Studies M14-867 and M14-868, all subjects (N = 147) with HCV GT1, GT2, GT4, GT5 and GT6 infection have achieved SVR_{12}, following 8 or 12 weeks of treatment and a high SVR_{12} rate of 96% has been achieved for GT3 infected subjects (107/111).

Study M15-410 is a Phase 2 study designed to assess the efficacy and safety of the combination of ABT-493 and ABT-530 in subjects who failed a prior DAA-containing therapy. Prior DAA treatment regimens among enrolled include SOF/LDV (n = 8), SMV + SOF ± RBV (n = 8), 3D ± RBV (n = 4), DSV + FDV + RDV ± RBV (n = 4), SAM + SMV (n = 2), TVR + PR (n = 8), BOC + PR (n = 10), DCV ± PR (n = 2). The most common NS3 RAVs at baseline include Q80 (n = 22), R155 (n = 4), and D168 (n = 4), and the most common NS5A RAVs at baseline include Q30 (n = 14) and Y93 (n = 10). Six out of 6 subjects on ABT-493 200 mg and ABT-530 120 mg, and 20 out of 22 subjects on ABT-493 300 mg and ABT-530 120 mg plus RBV 800 mg have achieved SVR_{12}. Twenty one out of 22 subjects (95%) who were treated with the ABT-493 300 mg and ABT-530 120 mg combination therapy have achieved SVR_{12}. A summary of the SVR rates of ABT-493/ABT-530 300 mg/120 mg in the Phase 2 Studies M14-867, M14-868 and M15-410 is presented in Table 6.

Table 6. SVR_{12} Rates of ABT-493/ABT-530 300 mg/120 mg in the Phase 2 Studies M14-867, M14-868 and M15-410

Treatment Arms	M14-867 Arm K	M14-868 Arm A	M14-868 Arm J	M14-868 Arm D	M14-868 Arm L	M14-868 Arm O	M14-867 Arm I	M15-410 Arm C
Genotype	GT1	GT2	GT2	GT3	GT3	GT3	GT4, GT5, GT6	GT1
Cirrhotic	Yes	No	No	No	No	Yes	No	No
Total N	34	25	54	30	53	28	34	22
PR-Exp	5	3	7	3	24	4	5	-
DAA-Exp	0	0	0	0	0	0	0	22
Duration (Weeks)	8	12	8	12	8 (TN)/ 12 (PR-Exp)	12 (TN)/ 16 (PR-Exp)	12	12
SVR_{12} (Overall)	100%	100%	100%	97%	96%	96%	100%	95%
SVR_{12} (TN)	100%	100%	100%	100%	100%	100%	100%	-
SVR_{12} (TE^)	100%	100%	100%	67%	92%	75%	100%	95%

DAA-EXP = direct acting antiviral-experienced; PR-Exp = pegIFN/RBV experienced; SVR_{12} = sustained virologic response 12 weeks post-treatment; TN = Treatment Naïve; TE = Treatment-experienced

^ TE include pegIFN experienced (PR-Exp) or DAA-experienced.

The combination therapy of ABT-493 and ABT-530 is well tolerated and the most frequently reported adverse events were fatigue, nausea, and headache (occurring in > 5% of subjects) with the majority being Grade 1 or 2 in severity. Among the 274 subjects who received at least one dose of study drug in the Phase 2 studies, Studies M14-867 and M14-868, there were 4 (1.5%) treatment-emergent SAEs reported: pneumonia, atrial fibrillation, B-cell lymphoma, and metastatic prostate cancer, and all assessed as having no reasonable possibility of being related to ABT-493 or ABT-530. Two subjects (0.7%; 2/274) discontinued due to treatment-emergent adverse events. One subject with history of irritable bowel disease discontinued due to Grade 2 AE of abdominal pain assessed as having a reasonable possibility of being related to both the DAAs and RBV. In all subjects with baseline ALT elevations in Studies M14-867 and M14-868, the ALT levels

were normalized or trended toward normal with DAA treatment, and there have been no on-treatment ALT elevations above baseline.

A total of 2,376 subjects were randomized or enrolled in the registrational studies or supportive Phase 2 studies to receive GLE 300 mg QD and PIB 120 mg QD. Of these, 2,369 subjects received at least 1 dose of study drug.

Sofosbuvir (SOF)

SOF is a nucleotide analog NS5B polymerase inhibitor active against all major genotypes. SOF is indicated for the treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen. The approved dose is 400 mg orally once daily, without regard to food.[45]

A study to assess the PK and safety of co-administration of 400 mg QD SOF in combination with ABT-493 400 mg QD and ABT-530 120 mg QD in healthy subjects (Study M14-532) showed minimal effect (≤ 16% change in central values) on the steady-state exposures of ABT-493 and ABT-530 compared to the administration of ABT-493/ABT-530 combination alone. SOF C_{max} and AUC_{0-24} central values were increased by 66% and 125%, respectively, compared to SOF alone, however, GS-331007 C_{max} and AUC_{0-24} were minimally affected (≤ 21% change in central values).

Comprehensive safety, efficacy and PK information is contained within the SOF USPI/SmPC/local label.

Ribavirin (RBV)

RBV is a guanosine analogue that has little or no effect on HCV RNA as monotherapy, but when combined with interferon-based therapies, RBV improves SVR rate over conventional or pegIFN monotherapy.[46,47]

RBV is a known teratogen (FDA category X). Pregnancy should be avoided following RBV therapy (Refer to Section 6.1.6). Comprehensive safety, efficacy and PK information is contained within the RBV USPI/SmPC/local label.

3.1 Differences Statement

Study M15-942 is the first study to investigate ABT-493/ABT-530 in combination with SOF and RBV as a retreatment option for subjects infected with HCV GT1 – 6, with or without HIV-1 co-infection, who experienced virologic failure following treatment with ABT-493/ABT-530 in a previous AbbVie HCV clinical trial, designated as the AbbVie HCV parent study. Subjects who have experienced virologic failure following treatment with 3D or 2D in an AbbVie HCV parent study may be enrolled at AbbVie's discretion.

3.2 Benefits and Risks

Benefits

Subjects who have experienced virologic failure following treatment with ABT-493/ABT-530, as well as treatment with 3D or 2D, are difficult patient populations to cure and need effective and safe options for retreatment. Study M15-942 is designed to retreat these subjects with an intensified regimen that contains ABT-493, an NS3/4A inhibitor; ABT-530, an NS5A inhibitor; SOF, an NS5B inhibitor and RBV, for either 12 weeks or 16 weeks.

One of the potential benefits of retreatment with ABT-493/ABT-530 plus SOF and RBV is that the co-administration of drugs of distinct mechanisms of action can potently inhibit the viral replication of HCV variants present in DAA treatment-experienced subjects effectively, thus leading to a higher cure rate.

ABT-493/ABT-530 demonstrates excellent antiviral activity with high genetic barrier to development of drug resistance which has been translated into high SVR_{12} rates in clinical studies.

The addition of SOF and RBV to ABT-493/ABT-530 provides additional mechanism(s) of action that may overcome resistant variants selected in subjects exposed to ABT-493/ABT-530 alone. The longer treatment duration of 16 weeks for cirrhotic subjects, subjects with GT3 infection, and subjects who have previously failed a PI-

and/or NS5Ai-containing regimen before experiencing virologic failure in an AbbVie HCV parent study is expected to improve the chances of achieving SVR_{12}.

SVR rates among HCV/HIV-1 co-infected patients treated with new, all-oral HCV DAA regimens are comparable to those observed in HCV-monoinfected patients, and this similar efficacy finding is anticipated following treatment with ABT-493/ABT-530. In addition, successfully treating these patients is expected to address the risk of increased disease progression in untreated HCV/HIV-1 co-infected patients (accelerated hepatic fibrosis progression and higher rates of liver decompensation and death compared to HCV monoinfection). Also, liver disease is a leading cause of non-AIDS-related mortality among HIV-1-infected patients.[25-27]

Risks

The likelihood of successfully retreating HCV infection with ABT-493/ABT-530 plus SOF and RBV is not known.

The safety profile of SOF and RBV are well established. Adverse events that are known as well as those not previously described may occur with the combination of ABT-493/ABT-530 plus SOF and RBV, 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 drug alone and the combination of ABT-493/ABT-530 plus SOF and RBV are detailed in Section 3.0 and in the Investigator's Brochure or product package inserts.

Additional risks associated with ABT-493/ABT-530 plus SOF and RBV, including the risks of toxicity, virologic failure, and development of resistance-associated variants (Section 5.6.4), appear to be limited and manageable based upon the available data.

Virologic failure criteria have been incorporated into the study to ensure subjects are exposed to appropriate durations of the regimen.

Given the potential benefits of expected high SVR_{12} rates in a population of subjects who failed multiple classes of DAAs, as well as the limited risks associated with the planned therapy, the risk-benefit assessment is favorable.

4.0 Study Objective

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

5.0 Investigational Plan

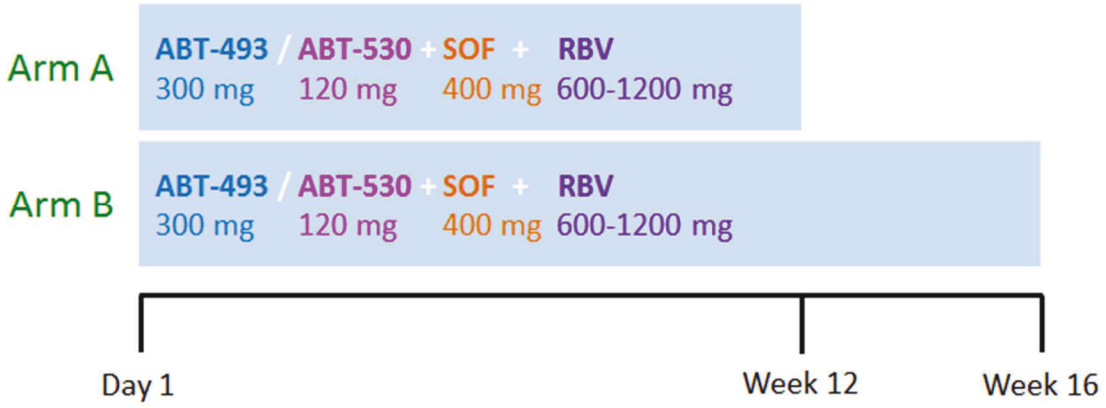
5.1 Overall Study Design and Plan: Description

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

It is anticipated that approximately 50 HCV infected subjects who have experienced virologic failure following treatment with ABT-493/ABT-530 or 3D or 2D regimens in one of the AbbVie HCV parent studies will be enrolled. Besides meeting the eligibility criteria (Section 5.2), additional subject eligibility to enroll in Study M15-942 will be evaluated at the discretion of AbbVie based upon the characteristics of subject's HCV infection, prior treatment history, and the evolving data from on-going clinical studies.

A study schematic (Treatment Period) is shown below in Figure 1.

Figure 1. Study Schematic (Treatment Period)



Arm A will enroll approximately 5 subjects, and Arm B will enroll approximately 45 subjects. Subjects will be allocated to one of two treatment arms based on HCV genotype, cirrhosis status, and treatment experience with PI and/or NS5Ai-containing regimens prior to enrolling in the AbbVie HCV parent study, as defined in Table 7 below.

Table 7. Treatment Arm Allocation in Study M15-942

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

* NC = non-cirrhotic; C = cirrhotic.

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

- Arm A: Subjects will receive orally ABT-493/ABT-530 300 mg/120 mg QD, SOF 400 mg QD, and RBV 600 mg to 1200 mg daily in two divided doses (based on baseline age and weight)* for 12 weeks.
- Arm B: Subjects will receive orally ABT-493/ABT-530 300 mg/120 mg QD, SOF 400 mg QD, and RBV 600 mg to 1200 mg daily in two divided doses (based on baseline age and weight)* for 16 weeks.

* As defined on Table 8.

Table 8. Ribavirin Dosing Recommendations

Age at Baseline (Years)	Body Weight at Baseline (kg)	Daily Dose (mg)	Number of 200 mg Tablets Per Period of the Day
≥ 18	< 75	1000	2 tablets A.M. + 3 tablets P.M.*
	≥ 75	1200	3 tablets A.M. + 3 tablets P.M.
≥ 12 and < 18	35 – 46	600	1 tablet A.M. + 2 tablets P.M.*
	47 – 59	800	2 tablets A.M. + 2 tablets P.M.
	60 – 74	1000	2 tablets A.M. + 3 tablets P.M.*
	≥75	1200	3 tablets A.M. + 3 tablets P.M.

* The A.M and P.M. pills can be taken in reverse order.

Alternative RBV dosing can be used if agreed upon by AbbVie TA MD prior to implementation.

All subjects administered at least one dose of study drugs will be followed for 24 weeks in the Post-Treatment Period to monitor for safety, HCV RNA, and the emergence and/or persistence of resistance-associated viral variants.

The planned duration of the study (excluding Screening) will be up to 40 weeks.

As this is an open-label study, safety will be reviewed by AbbVie. Virologic failure criteria for subject management, as detailed in Section 5.4.1.1, will be evaluated and applied by the investigator.

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 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 42 days following the Screening Visit to enroll into the study.

5.1.1.1 Rescreening

Subjects who test positive at Screening for any of the following parameters are not eligible to rescreen:

- Positive Hepatitis B surface antigen (HBsAg);
- A positive HIV-2 test;
- A positive serum pregnancy test (if female).

In addition, subjects who develop decompensated liver disease, including ascites noted on physical exam, hepatic encephalopathy or esophageal variceal bleeding during the screening period will not be eligible for rescreening.

Otherwise, subjects may be retested/rescreened only once without approval of the AbbVie Therapeutic Area Scientific Director (TA SD)/TA MD, as follows:

- Subjects who have exclusionary laboratory parameter(s) are allowed to retest within the screening period 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 who fail to enroll within 42 days of Screening, regardless of the reason for falling outside the 42-day screening window, may rescreen only once and must be rescreened for all eligibility criteria (except those noted below), not just those that were exclusionary.

Subjects may rescreen once for any other reason, with approval of the AbbVie TA SD/TA MD.

Subjects being rescreened do not need to be retested for HBsAg, HIV-2 Ab, HCV genotype and subtype, and FibroScan/liver biopsy.

5.1.2 Treatment Period

Prior to the Study Day 1 visit, after all eligibility criteria have been confirmed, subjects will be allocated via IRT into one of two treatment arms based on their HCV genotype, cirrhotic status, and prior treatment experience with PI- and/or NS5Ai-containing regimens before experiencing virologic failure in an AbbVie HCV parent study. Subjects will be administered study drugs at the site on Study Day 1, and provided with dosing instructions.

Study visits during the Treatment Period are detailed in Appendix C. Safety and tolerability will be assessed throughout the study. Laboratory testing will include chemistry, hematology, and urinalysis as specified in Table 10. Plasma samples for pharmacokinetic analysis and HCV RNA analysis will be collected as detailed in Section 5.3.1.1 and Section 5.3.3.1, respectively. Blood samples for optional pharmacogenetic analysis will be collected as detailed in Appendix C.

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

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

Virologic failure criteria will be evaluated and applied by the investigator as detailed in Section 5.4.1.1. Subjects meeting on-treatment virologic failure (OTVF) criteria will be discontinued from study drugs.

Subjects who discontinue from the study drugs during the Treatment Period regardless of the reason for discontinuation should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Appendix C and as described in Section 5.4.1.

Subjects who take at least one dose of study drug and complete or discontinue treatment will enter the Post-Treatment Period as detailed in Section 5.1.3.

5.1.3 Post-Treatment Period

All subjects who received at least one dose of study drug and either complete or discontinue treatment will be monitored for an additional 24 weeks following the last dose of study drug for safety, HCV RNA and the emergence, persistence of resistance-associated viral variants, and – for HCV/HIV-1 coinfected subjects – plasma HIV-1 RNA and HIV drug resistance.

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 Appendix C and Section 5.3.1.1.

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

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

5.2 Selection of Study Population

The study population consists of chronic HCV GT1 – 6-infected adult or adolescent subjects who experienced virologic failure while participating in an AbbVie HCV parent study. Subjects must meet all the inclusion criteria and none of the exclusion criteria. In addition, the eligibility of a subject to enroll in Study M15-942 will be evaluated at the discretion of AbbVie based upon the characteristics of the subject's HCV infection, prior treatment history, and the evolving data from on-going clinical studies.

5.2.1 Inclusion Criteria

1. Male or female subjects must be adults (18 years or more) or adolescents (12 to less than 18 years). Adolescent subjects must weigh at least 35 kg.
2. Subject must have experienced virologic failure during or after treatment with ABT-493/ABT-530 in an AbbVie HCV parent study. Subjects who have experienced virologic failure during or after receiving ombitasvir/paritaprevir/r + dasabuvir (3D), or ombitasvir/paritaprevir/r (2D) in an AbbVie HCV parent study may be enrolled at AbbVie's discretion. Treatment in the parent study must have been completed or discontinued at least 1 month prior to the Screening Visit.
3. If female, subject must be either
   - Postmenopausal, OR
   - Permanently surgically sterile, OR
   - Women of Childbearing Potential (CBP), practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 through at least 4 months after the last dose of study drug or as directed by the local RBV label, whichever is more restrictive.
4. If a male subject is sexually active with female partner(s) of CBP, he must agree to practice the protocol specified contraception (Section 5.2.4), from Study Day 1

through 7 months after the last dose of study drug, or as directed by the local RBV label, whichever is more restrictive.

5. Female subjects of CBP must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.

   Females not of CBP at Screening do not require pregnancy testing.

6. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

7. 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.

8. Cirrhotic subjects must have compensated cirrhosis, defined as a Child-Pugh score of ≤ 6 at Screening and:
   - No current or past evidence of Child-Pugh B or C Classification
   - No clinical history of liver decompensation, including ascites noted on physical exam, hepatic encephalopathy or esophageal variceal bleeding.

9. Cirrhotic subjects must demonstrate absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound (US), computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative US at Screening. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study,

In additional to Inclusion Criteria 1 to 9, subjects with HCV/HIV-1 co-infection must also meet the following criteria:

10. Subject must be:
    - Naïve to HIV treatment with any antiretroviral therapy (ART) and have no plans to initiate ART treatment while participating in this study, or

- On a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to Screening.
- The HIV-1 ART regimen must include at least one of the following ARV agents:
  - For cirrhotic and non-cirrhotic subjects:
    - Raltegravir (RAL) PO BID
    - Dolutegravir (DTG) PO QD or PO BID
    - Rilpivirine (RPV) PO QD
    - Elvitegravir/cobicistat (EVG/COBI) PO QD
  - For non-cirrhotic subjects:
    - Darunavir (DRV) co-administered with ritonavir (RTV) PO QD
    - Darunavir/cobicistat (DRV/COBI) PO QD
    - Lopinavir/ritonavir (LPV/r) PO BID

In addition to the above medications, subjects may take a nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI) backbone containing any of the following:

- Tenofovir disoproxil fumarate (TDF) PO QD
- Tenofovir alafenamide (TAF) PO QD
- Abacavir (ABC) PO QD or BID
- Emtricitabine (FTC) PO QD
- Lamivudine (3TC) PO QD or BID

Subjects receiving any other HIV-1 ART in addition to those noted above would not be eligible for enrollment in the study.

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

    Subjects on a stable ART regimen must have the following:

    - CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening;
    - and Plasma HIV-1 RNA < 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once (HIV-1 < 50 copies/mL) during the 12 months prior to Screening (by an approved

plasma HIV-1 RNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).

Rationale for Inclusion Criteria

1, 2, 8 – 11	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
3 – 5	RBV has known teratogenic effects. The impact of ABT-493 and ABT-530 on human pregnancies has not been established. However, assessment of the completed nonclinical reproductive toxicology studies indicates that there is no drug-related effect on teratogenicity/fetotoxicity. In addition, the compounds are non-genotoxic. No adequate human data are available to establish whether or not sofosbuvir poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of sofosbuvir at exposures greater than those in humans at the recommended human dose[16]
6, 7	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. History of severe, life-threatening or other clinically significant sensitivity to or inability to take any study drug or drug component.
2. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for 4 months after the last dose of study drug, or as directed per the local RBV label, whichever is more restrictive.
3. Male subject who is considering fathering a child or whose partner is pregnant during the study or for 7 months after the last dose of the study drug, or as directed per the local RBV label, whichever is more restrictive.
4. Positive test result at Screening for hepatitis B surface antigen (HBsAg).
5. Positive Human Immunodeficiency virus, type 2 (HIV-2) Ab at Screening.

6. Requirement for and inability or unwillingness to safely discontinue the medications or supplements listed in Table 9 at least 2 weeks prior to the first dose of any study drug.
7. Requirement for chronic use of systemic immunosuppressants during the study, including but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab).
8. Use of any of the following:
   - Any prohibited therapy including potent P-gp inducers (including, St. John's Wort, carbamazepine, phenytoin, and rifampin) within 2 weeks or 10 half-lives (whichever is longer) prior to study drug administration (Section 5.2.3.4).
   - Any medications that are contraindicated to be used in combination with SOF or RBV, as per local label.
9. Clinically significant abnormalities, other than HCV monoinfection or HCV/HIV-1 co-infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator, including, but not limited to:
   - Uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8% during Screening.
   - Active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
   - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection.
10. Treatment for an AIDS-Defining Condition (ADC) (Appendix D) within 6 months of Screening.
11. 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
- Steatosis or steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection

12. Screening laboratory analyses showing any of the following abnormal laboratory results:
    - ALT > 10 × ULN
    - AST > 10 × ULN
    - Albumin < 2.8 g/dL
    - International normalized ratio (INR) > 1.5, unless subject has known hemophilia or is on a stable anticoagulant regimen affecting INR
    - Hemoglobin < 10 g/dL, or as per local RBV label, if more restrictive.
    - Platelets < 50,000 cells per mm^3 for subjects aged ≥ 18 years, or < 40,000 cells per mm^3 for subjects aged < 18 years.
    - Calculated creatinine clearance < 30 mL/min
13. History of solid organ transplantation.
14. Receipt of any HCV treatment after failing the treatment regimen in the AbbVie HCV parent study.
15. Discontinuation of the prior HCV treatment in the AbbVie HCV parent study for reasons other than virologic failure (e.g., non-adherence, lost to follow-up, and/or the occurrence of an adverse event).
16. 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.
17. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-493, ABT-530, SOF, or RBV.

18. Subject who cannot participate in the study per local law.

19. Current enrollment in another interventional clinical study or previous enrollment in this study (except the AbbVie HCV parent study). Concurrent participation in a non-interventional, epidemiologic or registry trials may be permitted with approval by the AbbVie TA SD/TA MD.

20. Subject has confirmation of HCV reinfection at screening visit (as defined in Section 5.4.1.1).

Rationale for Exclusion Criteria

1, 2, 3, 8, 10 – 12, 17 – 19	In order to ensure safety of the subjects throughout the study
6, 7, 13 – 19, 20	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
4, 9, 11	To exclude subjects with liver diseases other than HCV
5	To exclude subjects with HIV-2 co-infection

5.2.3 Prior and Concomitant Therapy

Use of medications/supplements (including prescription or over-the-counter, vitamins and/or herbal supplements) or vaccines from the time of signing the informed consent through the Treatment Period and 30 days after study drugs are stopped, must be recorded in the electronic case report form (eCRF) at each study visit indicated in the Treatment Period (Appendix C) 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. After 30 days post-treatment, during the Post-Treatment Period, only antiviral therapies related to the treatment of HCV and/or

HIV and medications prescribed in association with a serious adverse event (SAE) will be recorded in EDC.

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

5.2.3.1 Prior HCV Therapy

The HCV drug treatment regimen and its duration given as a part of the subject's participation in an AbbVie HCV parent study, as well as all other past HCV treatment regimens and their durations received by the subject, will be recorded in the eCRF.

5.2.3.2 Prior and Concomitant HIV-1 Therapy

If a subject is on an HIV-1 ART regimen, it must include at least one of the ARV agents defined on Inclusion Criterion 10 (Section 5.2.1).

Subjects will maintain the same dose and dosing interval of their HIV-1 ART regimen upon initiating the study drugs regimen.

Subjects must remain on the same HIV-1 ART regimen for the entire Treatment Period. Any change to an allowed HIV-1 ART regimen during the Treatment Period must be discussed with the AbbVie TA SD/TA MD prior to the change, unless the change is being made to address an immediate safety concern.

Subjects receiving any other HIV-1 ART in addition to those listed in Inclusion Criterion 10 (Section 5.2.1) would not be eligible for enrollment in the study.

5.2.3.3 Other Concomitant Therapy

Subjects should be on a stable dose of concomitant medications for at least 14 days 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.

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, up to 14 days following discontinuation of study drugs, if applicable.

Flu shots and all essential vaccinations are allowed during Screening through the Post-Treatment Period for all subjects. Flu shots and vaccinations may affect plasma HIV-1 RNA levels.

5.2.3.4 Prohibited Therapy

Medications or supplements prohibited to be administered with ABT-493/ABT-530 are listed in Table 9. For subjects in the study in countries where ABT-493/ABT-530 (glecapravir/pibrentasvir) has received marketing authorization, any medications in the local label that are contraindicated to be administered with ABT-493/ABT-530 (glecapravir/pibrentasvir) are also considered to be prohibited medications. Subjects must be able to safely discontinue any prohibited medications or supplements at least 14 days 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 14 days following discontinuation of study drugs. The Informed Consent Form must be signed and dated prior to discontinuing any prohibited medications or supplements for the purpose of meeting study inclusion criteria.

Table 9. Medications and Supplements Prohibited with ABT-493/ABT-530 Administration

Medication or Supplement Name
Red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine
Tipranavir/r, atazanavir, efavirenz, etravirine, nevirapine
Ethinyl estradiol

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. After signing the informed consent form, subjects receiving these statins should either (a) switch to pravastatin or rosuvastatin at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug or (b) interrupt statin therapy throughout the treatment period beginning at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug and until 14 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to either 1) reduce or limit the pravastatin or rosuvastatin dose in accordance with the ABT-493/ABT-530 (glecapravir/pibrentasvir) product label (if approved in the country) when taking with the study drug; or 2) reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug, if ABT-493/ABT-530 (glecapravir/pibrentasvir) is not yet approved in the country.

In addition, refer to the current package insert or product label for SOF and RBV for a complete list of medications prohibited to be used with those drugs, which should not be used at least 14 days prior to the first dose of any study drug, throughout the entire Treatment Period and for 14 days following discontinuation of study drugs.

Contraceptives and/or hormonal replacement therapies containing only progestins/progestogens (such as those containing norethindrone, desogestrel, or levonorgestrel) or those containing progestins/progestogens with non-ethinyl estradiol estrogens (e.g., esterified or conjugated) may be used with ABT-493/ABT-530 at the discretion of the Investigator.

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

For HCV/HIV-1 coinfected subjects, the investigator must refer to the current package insert(s) or product label(s) of a subject's ART regimen for a complete list of medications prohibited to be used with those drugs, which should not be used at least 14 days prior to the first dose of any study drug and not use these during the entire Treatment Period and for 14 days following discontinuation of study drugs.

Use of hematopoietic growth factors is permitted during this study only with the approval of the TA SD/TA MD. Management of hematologic growth factor therapy is the responsibility of the investigator; growth factors will not be provided by AbbVie, and AbbVie will not reimburse for the expense of growth factors or their use.

Investigators should refer to the package inserts for erythropoiesis stimulating agents for additional information regarding their use.

5.2.4 Contraception Recommendations

Female Subjects

If female, subject must be either postmenopausal defined as:

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

OR

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

OR

Females subjects of CBP must be:

- Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 4 months after the last dose of study drug, or as directed by the local RBV label, whichever is more restrictive.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
  - Bilateral tubal occlusion/ligation or bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
  - Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the CBP trial participant.
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
  - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence] e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

Male Subjects

Male subjects who are sexually active with a female partner of CBP, even if the male subject has undergone a successful vasectomy, must agree to use condoms from Study Day 1 through at least 7 months after the last dose of study drug and his female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female

study subjects of childbearing potential). If the local RBV label for the subject has more restrictive recommendations, they must be followed instead.

Male subject must agree not to donate sperm from Study Day 1 through at least 7 months after the last dose of study drug (or as directed by the local RBV label, whichever is more restrictive).

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 Appendix C.

5.3.1.1 Study Procedures

Informed Consent and RBV Information

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. All subjects will be given the RBV Medication Guide (where applicable/locally available). Male subjects will be given an additional copy of the RBV Medication Guide (where applicable/locally available) to share with their female partner(s) (where applicable/locally available). Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical History

The subject's medical history including history of tobacco, alcohol use and drug use, recorded in the AbbVie HCV parent study, will be updated at the Screening Visit with any relevant information that was not collected in the previous AbbVie study and any new medical history that occurred between the end of the previous AbbVie study and this study. In some cases, the medical history recorded in the previous AbbVie study will be electronically transferred into the eCRFs in this study and in other cases it will need to be

manually entered into the eCRFs by the site due to differences between the medical history eCRFs for the previous AbbVie study and the current study. The subject's medical history will also be updated, as needed, at the Study Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Appendix C, or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, 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 the first dose will be recorded as adverse events.

Height will be measured only at Screening.

Vital Signs and Weight

Body temperature, blood pressure, waist circumference, pulse and body weight will be measured at each study visit as specified in Appendix C or upon subject discontinuation. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes and prior to blood collection. The subject will wear lightweight clothing and no shoes during weighing.

Pregnancy Testing

A serum and urine pregnancy test will be performed for all female subjects of childbearing potential at Screening and Day 1. Additional urine pregnancy tests will be performed every 4 weeks, starting at Day 1 (prior to enrollment) during the treatment period, including at the last treatment period visit and until 4 months after the last study drug dose (or as directed by local RBV label, whichever is more restrictive), as indicated in Appendix C. Determination of postmenopausal status will be made during the Screening period, based on the subject's history.

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

12-Lead Electrocardiogram

A 12-lead resting ECG will be obtained at Screening. The ECG should be performed prior to blood collection.

The ECGs 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 10 at the visits indicated in Appendix C.

Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast (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. 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
8211 SciCor Drive
Indianapolis, IN 46214 USA
(For sites in North America)

Covance
7 rue Moise-Marcinhes
1217 Meyrin
Geneva Switzerland
(For sites in Europe)

Covance (Asia) Pte Ltd
1 International Business Park
#01-01 The Synergy
Singapore 609917
(For sites in Asia, Australia and New Zealand)

Table 10. 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[a] Activated partial thromboplastin time (aPTT)	Blood Urea Nitrogen (BUN) Uric Acid Creatinine Creatinine clearance (Cockcroft-Gault calculation) eGFR (MDRD method) Total bilirubin[a] Direct and indirect bilirubin Serum Alanine Aminotransferase (ALT) Serum Aspartate Aminotransferase (AST) Alkaline phosphatase Gamma-glutamyl transferase (GGT) Total protein Albumin[a] Glucose Total insulin Sodium Potassium Calcium Inorganic phosphorus Chloride Bicarbonate Magnesium Cholesterol Triglycerides Low Density Lipoproteins (LDL)[b,c,d] High Density Lipoprotein (HDL)[b,d]	Anti-HIV Ab[e] FSH (all females)[e] Urine and Serum Human Chorionic Gonadotropin (hCG) for females[f] HCV RNA HIV-1 RNA[b] Hemoglobin A1C[e] HCV genotype and subtype[e] Pharmacogenetic sample (optional) Alpha2-macroglobulin[g] Haptoglobin[g] Apolipoprotein A1[g] CD4, CD4%[b] CD8, CD8%[b] CD4:CD8[b] Anti-Hepatitis A Virus IgM[h] Anti-Hepatitis A Virus Total[h] Anti-Hepatitis E Virus IgG[h] Anti-Hepatitis E Virus IgM[h] HEV RNA[h] HBsAg[e,h] Anti-HBc IgM[h] Anti-HBc Total[h] Anti-HBs[h] HBV DNA[h]
Urinalysis		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Microscopic (reflex) Albumin[i]		

a. Also a component of the Child-Pugh Assessment (along with ascites and encephalopathy).

b. Only for known HCV/HIV-1 co-infected subjects.

c. Directly measured.

d. Performed only at Day 1.

e. Performed only at Screening.

f. Females not of CBP at Screening do not require pregnancy testing as defined in Section 5.2.1 Criterion 5.

Table 10. Clinical Laboratory Tests (Continued)

g. Component of FibroTest and collected only if needed during the Screening Period.
h. Performed for management of transaminase elevation (Section 6.1.7.5).
i. Collected for confirmed Creatinine Clearance < 50 mL/min, if clinically indicated as defined in Section 6.1.7.6.

For any laboratory test value outside the reference range that the investigator considers to be 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 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.

Hepatitis B and HIV Screen

HBsAg (hepatitis B surface antigen) and anti-HIV Ab will be performed at Screening. 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. The HBsAg results will be reported by the central laboratory to the clinical database.

Liver Diagnostic Testing

Subjects categorized as **cirrhotic** in the AbbVie HCV parent studies will be categorized as being cirrhotic in this study.

Subjects categorized as **non-cirrhotic** in the AbbVie HCV parent studies, who do not have a qualifying liver biopsy showing absence of cirrhosis within the previous 12 months from Screening or qualifying FibroScan showing absence of cirrhosis with the previous 6 months from Screening, but who otherwise meet all of the inclusion criteria and none of

the exclusion criteria will undergo liver biopsy or non-invasive testing (FibroTest/APRI or FibroScan) prior to enrollment. Selection of liver biopsy or non-invasive testing performed should be based on local standard practice.

Subjects must be documented as non-cirrhotic or cirrhotic defined as meeting one of the following criteria:

Non-Cirrhotic

A liver biopsy within 12 months prior to or during Screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4; or

A FibroScan® score of < 12.5 kPa within ≤ 6 months of Screening or during Screening period (FibroScan® must be approved by the local regulatory agency to qualify for entrance criteria); or

A Screening FibroTest score of ≤ 0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) < 1.

Cirrhotic

Previous histologic diagnosis of cirrhosis on liver biopsy, e.g., METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of > 3, Ishak score of > 4 or on a liver biopsy conducted during Screening; or

A FibroScan® score of ≥ 12.5 kPa at any time prior to Screening or during Screening period (FibroScan® must be approved by the local regulatory agency); or

A Screening FibroTest result that is ≥ 0.75 and an APRI > 2.

In the absence of a definitive diagnosis of presence or absence of cirrhosis by FibroTest/APRI using the above criteria (indeterminate FibroTest [0.48 < result < 0.75], or conflicting FibroTest and APRI results [e.g., FibroTest ≤ 0.48, but APRI

≥ 1]), a liver biopsy or FibroScan® is required. Liver biopsy results will supersede Fibrotest/APRI or FibroScan® results and be considered definitive.

Subjects who are categorized as cirrhotic in this study according to the criteria above must also meet Inclusion Criteria 8 and 9.

When performed within the specified timeframes, the result of the liver biopsy supersedes the results of FibroScan and FibroTest/APRI and result of FibroScan supersedes the results of FibroTest/APRI.

Child-Pugh (Child-Turcotte-Pugh) Score and Category

The Child-Pugh (Child-Turcotte-Pugh) score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments) as shown in Table 11. Child-Pugh score will be determined only for subjects with compensated cirrhosis at the visits indicated in Appendix C.

Table 11. Child-Pugh (Child-Turcotte-Pugh) Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/L (mg/dL)	< 34.2 (< 2)	34.2 – 51.3 (2 – 3)	> 51.3 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 – 35 (2.8 – 3.5)	< 28 (< 2.8)
INR	< 1.7	1.7 – 2.3	> 2.3
Ascites*	None	Slight	Moderate to severe
Hepatic encephalopathy**	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (or refractory)

* None; Slight ascites = Ascites detectable only by ultrasound examination; Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen; Severe ascites = Large or gross ascites with marked abdominal distension.

** Grade 0: normal consciousness, personality, neurological examination, electroencephalogram; Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves; Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves; Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves; Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

Clinical Assessment of Hepatic Decompensation

A clinical assessment of hepatic encephalopathy and ascites will be performed only for subjects with compensated cirrhosis at Study Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since screening.

Hepatocellular Carcinoma Screening: Liver Ultrasound

HCC screening will be required as a protocol-specified study procedure only at the Screening Study Visit and at the last Post-treatment Study Visit, as indicated in Appendix C, for subjects with compensated cirrhosis only. Between those visits, HCC screening should be performed according to standard of care.

At the Screening Study Visit and at the last Post-treatment Study Visit, subjects with compensated cirrhosis will be required to perform a liver ultrasound to screen for HCC,

unless the subject has a historical liver ultrasound, CT or MRI performed for HCC screening within 3 months prior to those visits, in which case the result of the historical US, CT or MRI will be used as the result for that Study Visit assessment. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. Alternate methods of screening for HCC (i.e., MRI or CT) at a study visit should be discussed with the TA MD.

Enrollment and Assignment of Subject Numbers

All screening activities must be completed and reviewed prior to enrollment. Subjects who meet the eligibility criteria will proceed to enrollment via the IRT system on Day 1 (Treatment Period). Subject numbers will be unique 5-digit numbers starting with 10001. The first 3 digits will represent the investigative site and the last 2 digits will represent the subjects screened at that site. Enrolled subjects will keep their subject number throughout the study.

Study Drug Compliance for Kits

Bottles of ABT-493/ABT-530, 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, SOF and RBV. At each drug accountability visit in Appendix C, the overall number of tablets of ABT-493/ABT-530, SOF and RBV remaining in each bottle will be recorded in the source and transferred to the IRT system along with the date of reconciliation.

HCV Genotype and Subtype

Plasma samples for HCV genotype and subtype will be collected at Screening. Genotype and subtype will be assessed using the Versant® HCV Genotype Inno LiPA Assay, Version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY). If the LiPA assay is unable to genotype/subtype a sample, its genotype/subtype will be determined by a Sanger sequencing assay of a region of the NS5B gene (Covance).

HCV RNA Levels

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

HCV Resistance Testing Sample

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

Archive Serum and Plasma Sample

Archive serum and plasma samples will be collected at the study visits, indicated in Appendix C. Archive serum and 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, biomarkers of inflammation or fibrosis, and other possible predictors of response including biomarker for other causes of liver diseases, as determined by AbbVie.

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

Study Drug Dosing Card

Subjects will be provided with self-administration instructions and study drug dosing cards to record the exact date, time (record to the nearest minute) and number of tablets of study drug administration (ABT-493/ABT-530, SOF, and RBV) for the last 2 doses of each study drug taken prior to the scheduled pharmacokinetic sample collection during the Treatment Period.

The site staff will record the information about the last 2 doses taken prior to the scheduled pharmacokinetic sample collection from the study drug dosing card into the eCRF. In the event that the dosing card 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 pharmacokinetic evaluation blood samples are taken, the following procedures should be performed:

- The study coordinator should make sure the subject is given the dosing card at the visits listed in Appendix C.
- The Investigator or designee will contact the subject approximately 2 days before the scheduled visit date to review the importance of proper study drug administration relative to the pharmacokinetic blood collection and documentation of dosing times on the dosing card. The date and time of the contact will be entered into the subject's source documents.
- The completed dosing card will be collected by the Investigator or designee on the day of the visit and be kept as a source record of dosage administration times documented in the eCRF.

Flow Cytometry, HIV RNA and HIV Resistance Testing Samples

For subjects with HCV/HIV-1 coinfection, samples for plasma HIV-1 RNA levels and flow cytometry (including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]) will be obtained at the times specified in Appendix C. Plasma HIV-1 RNA will be measured by the central laboratory using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0 HIV-1 Assay. Results below the LLOD are reported as: "Not Detected." Subjects will also have blood samples drawn and archived at the study visits indicated in Appendix C. These samples may be used for other analyses including drug resistance testing. These samples may be tested at the discretion of AbbVie.

If a HIV-1 RNA level result of a subject on stable HIV-1 ART is ≥ 200 copies/mL, the subject's HIV-1 RNA is to be repeated as noted in Section 5.4.1.2. At the time the repeat

plasma HIV-1 RNA is drawn, a sample should be obtained for HIV-1 genotypic resistance testing. If the subject's repeat HIV-1 RNA is ≥ 500 copies/mL, the sample obtained for HIV-1 genotypic resistance testing will be analyzed.

HIV-1 protease (PR), reverse transcriptase (RT) and integrase (IN) sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assay.

If the subject's repeat HIV-1 RNA is < 200 copies/mL, then the subject will resume routine plasma HIV-1 RNA assessments as shown in Appendix C, and described in Section 5.4.1.1.

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

5.3.1.2 Meals and Dietary Requirements

All study drugs should be dosed together and each dose should be taken with food.

5.3.1.3 Collection and Handling of Pharmacogenetic Exploratory Research Samples

Subjects will have the option to provide samples for optional pharmacogenetic exploratory research. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research.

Optional whole blood samples for DNA and RNA isolation will be collected on Day 1 and Post-Treatment Week 12 from each subject who consents to provide samples for exploratory research. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.0.

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

companies working with AbbVie) will store the optional pharmacogenetic exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-493/ABT-530 (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

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, primary metabolite of SOF (GS-331007), and RBV will be collected by venipuncture at each study visit indicated below and in Appendix C.

- All Treatment Period visits except for Study Day 1: two samples (4 mL each) will be collected without regard to the time. 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.

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, primary metabolite of SOF (GS-331007) and RBV will be provided by the central laboratory, the Sponsor, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), RBV, and archive serum and 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, primary metabolite of SOF (GS-331007), and RBV samples to the reference laboratories following separately provided instructions.

5.3.2.4 Measurement Methods

Plasma concentrations of ABT-493 and ABT-530, SOF, GS-331007 and RBV 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 Day 1 through 24 weeks after completion of treatment.

5.3.3.1 Primary Variable

The primary efficacy variable is SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm, and overall.

5.3.3.2 Secondary Variables

The secondary efficacy variables are:

- The percentage of subjects with HCV on-treatment virologic failure in each treatment arm and overall.
- The percentage of subjects with HCV virologic relapse in each treatment arm and overall.

5.3.4 Resistance Variables

For all subjects receiving study drug, the variants at signature resistance-associated amino acid positions at baseline identified by next generation sequencing (NGS) will be compared to the appropriate prototypic reference sequence.

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

5.3.5 Safety Variables

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

5.3.6 Pharmacokinetic Variable

Individual plasma concentrations of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), and RBV will be tabulated and summarized. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.7 Pharmacogenetic Exploratory Research Variables

Optional pharmacogenetic samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. The results from these analyses are exploratory in nature and may not be included with the study report.

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

If a subject is discontinued from study drugs or during 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 RBV (if applicable) to that subject must be discontinued immediately. DAAs may be continued at the Principal Investigator's discretion after discussion with the subject, if the benefit of continuing DAAs is considered to outweigh the risk. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. Subjects will be monitored for SVR in

the Post-Treatment Period as described in Section 5.1.3. The investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry.

5.4.1.1 HCV Virologic Failure Criteria

The following criteria will be considered evidence of OTVF, for the purposes of subject management, leading to discontinuation of study drug:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurement of > 1 log10 IU/mL above nadir) at any time point during study drug treatment; or
- Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during study drug treatment.

Confirmatory testing should be completed as soon as possible and the subject should remain on study drug treatment until the OTVF criterion has been confirmed. Subjects with confirmed OTVF 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 substitutions until 24 weeks post-treatment (Appendix C).

Post-treatment relapse is defined as confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any post-treatment visit, for subjects who completed treatment (defined as study drug duration ≥ 77 days for subjects who received 12 weeks or ≥ 103 days for subjects who received 16 weeks) and had HCV RNA < LLOQ at the final treatment visit, excluding cases of reinfection, as defined below. HCV reinfection is defined as confirmed HCV RNA ≥ LLOQ after the end of treatment in a subject who had HCV RNA < LLOQ at Final Treatment Visit, along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis performed by the sponsor of the HCV NS3, NS5A, and/or NS5B gene sequences. Reinfection in the case of the same HCV subtype is defined as a clade switch, as indicated by the lack of clustering between the

baseline and post-treatment sequences by phylogenetic analysis. If phylogenetic analysis is not possible due to technical difficulties, HCV reinfection may be determined with a confirmed HCV genotype or subtype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

5.4.1.2 Failure to Maintain HIV Virologic Suppression

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

The criteria for failure to maintain HIV virologic suppression among subjects on stable ARTs is as follows:

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

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

During the Treatment Period, subjects with confirmed failure to maintain HIV-1 RNA suppression should continue HCV study drug treatment unless there is a requirement for prohibited concomitant medications (Section 5.2.3.2) to construct a new HIV ART regimen.

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

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

5.4.2 Discontinuation of Entire Study

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

5.5 Treatments

5.5.1 Treatments Administered

Each dose of study drug (ABT-493/ABT-530, SOF, and RBV) will be dispensed in the form of tablets at the visits listed in Appendix C. The date and time of dosing will be recorded to the nearest minute in the source documents (or study drug dosing card) and the eCRF for the 2 days immediately prior to each study visit starting prior to the Week 2 visit.

AbbVie will provide ABT-493/ABT-530 as 100 mg/40 mg film-coated tablets. ABT-493/ABT-530 will be taken orally as three tablets QD (total daily dose of 300 mg/120 mg) and with food.

AbbVie will provide SOF as 400 mg tablets. SOF will be taken orally as 1 tablet QD, with food.

AbbVie will provide RBV as 200 mg tablets. RBV dosing is determined based on the age and weight of the subject at the Day 1 visit, as described in Table 8. RBV should be taken

with food. The RBV dose established at Day 1 should be maintained throughout the entire treatment, regardless of ulterior changes in age or weight, unless a dose modification is needed due to toxicity (see Section 6.1.7).

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).

In the event that there is an issue with the study drug supply during the Treatment Period, commercial drug may be provided only with prior AbbVie approval, so that the subject does not experience treatment interruptions. If commercial drug is provided, AbbVie will provide instructions for documentation.

5.5.2 Identity of Investigational Products

Information about the study drugs to be used in this study is presented in Table 12.

Table 12. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
ABT-493/ABT-530	AbbVie	Oral	Film-coated Tablet	100 mg/40 mg
Sofosbuvir	Gilead	Oral	Film-coated Tablet	400 mg
Ribavirin	Roche or Generic Manufacturer	Oral	Film-coated Tablet	200 mg

5.5.2.1 Packaging and Labeling

All study drugs will be supplied in bottles.

Each bottle will be labeled as required per country requirements.

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

5.5.2.2 Storage and Disposition of Study Drug

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

* Please refer to clinical label for detailed storage conditions.

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. Subjects will be allocated to one of two arms based on their HCV genotype (1 to 6), cirrhosis status (presence/absence), and prior treatment experience with PI- and/or NS5Ai-containing regimens before experiencing virologic failure in an AbbVie HCV parent study. For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive a unique study drug kit numbers. The study drug kit numbers will be assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

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

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

5.5.4 Selection and Timing of Dose for Each Subject

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

ABT-493/ABT-530 (3 tablets) will be dosed QD with food.

SOF (1 tablet) will be dosed QD, at the same time as ABT-493/ABT-530.

RBV (3 to 6 tablets based on age and weight of the subject at Day 1) will be dosed twice daily with food. For example, if a subject takes 5 tablets of RBV per day, 2 tablets should be taken in the morning, and 3 tablets should be taken in the evening. One of the two daily RBV doses will be taken at the same time as ABT-493/ABT-530 and SOF. The other RBV dose should be taken approximately 12 hours apart.

The timing of study drugs administration should be kept consistent during the treatment period.

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.

At each study visit after Day 1 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 Appendix C, study site personnel will assess subject compliance by inspecting the contents of the bottles and record the status of each one, as well as the exact number of remaining tablets of ABT-493/ABT-530, SOF and RBV 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. 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, POR 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 bottle 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 bottle is damaged, the subject will be requested to return the remaining study drug to the site. Replacement study drug may only be dispensed to the subject by contacting the IRT system. Study drug replacement(s) and an explanation of the reason for the misplaced or damaged study drug(s) will be documented within the IRT system. Study drug start dates for each drug and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each bottle, number of tablets remaining in each bottle

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

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is an open-label, non-randomized, multicenter study exploring the efficacy and safety of the combination regimen of ABT-493/ABT-530 plus SOF and RBV in subjects with chronic HCV GT1 – 6 infection who experienced virologic failure in HCV treatment in an AbbVie HCV parent study.

The primary efficacy is measured by the percentage of patients achieving SVR_{12} in each treatment arm. The study design will provide additional data on ABT-493/ABT-530 in combination with SOF and RBV, such as response rates in subjects infected with different HCV genotypes, with or without cirrhosis, the PI and/or NS5Ai treatment experience prior to the AbbVie HCV parent study pharmacokinetics, resistance, and the nature of virologic failure (e.g., OTVF or post-treatment relapse).

No control group is included in this study. This study does not aim to establish non-inferiority or superiority to the standards of care, thus a comparator arm is not needed.

5.6.2 Appropriateness of Measurements

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

5.6.3 Suitability of Subject Population

This study will enroll subjects infected with chronic HCV GT1 – 6 who experienced virologic failure following treatment with ABT-493/ABT-530, 3D or 2D regimens in an AbbVie HCV parent study, in order to assess the efficacy, safety of ABT-493/ABT-530 plus SOF and RBV as a retreatment regimen.

5.6.4 Selection of Doses in the Study

5.6.4.1 Rationale for Dose Selections

HCV infected patients who were treated and experienced virologic failure in an AbbVie HCV parent study, will be treated with ABT-493/ABT-530 300 mg/120 mg in combination with SOF 400 mg and weight-based RBV for 12 or 16 weeks in the current protocol. The dose of 300 mg/120 mg of ABT-493/ABT-530 was selected based on multiple HCV clinical trials including Studies M14-867, M14-868 and M15-410 in order to optimize efficacy of the combination while maintaining an acceptable safety profile, is consistent with the dose used in AbbVie HCV Phase 3 studies and is the approved dose for commercial use.

In Studies M14-867 and M14-868, high SVR rates have been achieved for the combination of ABT-493 300 mg and ABT-530 120 mg (Table 6). All subjects (N = 147) with HCV GT1, GT2, GT4, GT5 and GT6 infection have achieved SVR_{12}, following 8 or 12 weeks of treatment and a high SVR_{12} rate of 96% has been achieved for GT3 infected subjects (107/111). In Study M15-410 Part 1, 21 out of 22 subjects (95%) who were previous DAA-experienced and treated with the ABT-493 300 mg and ABT-530 120 mg combination therapy in the study have achieved SVR_{12}.

ABT-493 and ABT-530 regimens including the ABT-493/ABT-530 300 mg/120 mg QD regimen used in the current study 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, ALT levels normalized or trended toward normal with DAA treatment, and there have been no on-treatment ALT elevations above baseline grade.

SOF, an HCV nucleotide analog NS5B polymerase inhibitor, is approved for use at a dose of 400 mg per day. At this dose, SOF has been investigated in various studies in combination with RBV, pegIFN/RBV, and with the protease inhibitor simeprevir and the NS5A inhibitors DCV and LDV with or without RBV in cirrhotic and non-cirrhotic subjects, including those with prior failure of pegIFN and a protease inhibitor.[48,49] This dose has been shown to demonstrate significant antiviral activity with only modest treatment limiting toxicities and a safety profile that is similar to that of the AbbVie DAA's regimen. Therefore this dose will used in this study.

Weight based RBV, 600 mg to 1200 mg, will be dose-divided to twice daily. This dose is approved for treatment of adult and adolescent patients with chronic HCV infection in combination with pegIFN. The same dose is selected for this study because its safety profile has been well characterized when administered with pegIFN, including incidence of hemolytic anemia, and there are well-defined dose reduction criteria in the event of RBV-induced anemia as noted in Section 6.1.7.4. In addition, the RBV dose was studied in the absence of pegIFN in adults in Studies M12-267, M12-746, M12-998, M11-652, M11-646, M13-098, M13-389, M13-961, M14-002, and M14-004, and in adolescents in Study M14-748, and the RBV dose was found to be generally safe and well tolerated and resulted in high SVR rates. It has been demonstrated that for previous virologic failures, the inclusion of additional drugs that have different mechanisms of action in the combination retreatment regimen will increase the probability to achieve SVR.[50]

5.6.4.2 Rationale for Duration Selections

HCV infected patients who were treated and experienced a virologic failure in an AbbVie HCV parent study, will receive a regimen of ABT-493/ABT-530 in combination with SOF 400 mg and weight based RBV for 12 or 16 weeks in the current protocol. Treatment duration for the study was selected based on available data from Study M15-410 and it is dependent upon the subject's HCV genotype, cirrhotic status and

prior treatment experience with PI- and/or NS5Ai-containing regimens before experiencing HCV virologic failure in an AbbVie HCV parent study. In Part 1 of Study M15-410, the efficacy and safety of ABT-493 and ABT-530 with or without RBV in adults with chronic HCV GT1 infection without cirrhosis who previously failed treatment with a DAA-containing regimen were assessed. The interim results from this study, as summarized in Section 3.0, demonstrate high SVR_{12} rates (mITT rates of 95 – 100%) following a 12-week treatment regimen of ABT-493 and ABT-530 with or without RBV. In the current study, the addition of SOF and RBV to ABT-493/ABT-530 offers multiple mechanisms of action in the retreatment regimen and will increase the probability to achieve SVR following similar treatment duration.

In order to increase the probability to achieve SVR for subjects who are more difficult to treat, such as subjects with HCV GT3 infection, subjects with compensated cirrhosis and subjects who previously failed PI and/or NS5Ai-containing regimens prior to experiencing a virologic failure in an AbbVie HCV parent study, the treatment duration will be extended to 16 weeks. Since ABT-493/ABT-530 has pangenotypic activity, subjects with mixed infections and undetermined genotypes will be allowed to be treated in this study. The extended treatment duration of 16 weeks for subjects with GT3 infection was based on the study design of Part 3 of Study M14-868. In Part 3 of Study M14-868, GT3-infected subjects who were treatment-naïve are allocated to the 12 week arm, GT3-infected subjects who were IFN-experienced with compensated cirrhosis are allocated to the 16 week arm, GT3-infected subjects who were IFN-experienced subjects without compensated cirrhosis are allocated at a 1:1 ratio to the 12 week and 16 week treatment arms. To be consistent with the rationale of duration selection in Study M14-868, a longer treatment duration of 16 weeks with an intensified regimen of ABT-493/ABT-530 in combination with SOF and RBV is selected in Study M15-942 for subjects with GT3 infection, in order to increase the probability to achieve SVR in HCV GT3 infected subjects who have already failed a DAA-containing regimen.

Subjects with compensated cirrhosis have historically required longer treatment durations versus patients without cirrhosis. The ABT-493/ABT-530 regimen was evaluated for 12 week treatment duration in Study M14-172 for subjects with HCV GT1, 2, 4, 5, and 6 infection with compensated cirrhosis, who are either treatment-naïve, or PI- and NS5Ai-naïve. In Study M14-867, subjects infected with HCV GT1 with cirrhosis were evaluated following an 8 week treatment duration with ABT-493/ABT-530. All subjects who have completed the treatment (33 of 34) have achieved SVR. One subject prematurely discontinued at treatment Week 4 due to an AE, and at the time of discontinuation, the subject had no detectable virus.

Subjects who failed multiple DAA regimens are considered to be a difficult to treat patient population. The ABT-493/ABT-530 regimen was evaluated for a 12 week and 16 week treatment duration in Study M15-410, Part 2 for DAA treatment-experienced subjects with HCV GT1, 4, 5, and 6 infection with or without compensated cirrhosis. It is anticipated that a treatment duration of 16 weeks with ABT-493/ABT-530 in combination with SOF and RBV for subjects who have failed multiple DAA treatment regimens will maximize the probability of achieving SVR, and reduce the chance of HCV virologic failures across genotypes.

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 Sections 6.1 through 6.1.7.6. 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 previously reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are usually not considered to be adverse events or serious adverse events (SAE). However, laboratory abnormalities or changes in vital signs that result in study drug discontinuation or

interruption, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.1.7 regarding toxicity management) and/or are deemed clinically significant by the investigator should be recorded as AEs or SAEs as defined in Section 6.1.1.1 and Section 6.1.1.2.

An elective surgery/procedure scheduled to occur during the 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 due to worsening of the pre-existing condition), 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 AE meets any of the following criteria, it is to be reported to AbbVie as a 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

CTC AE 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

Assessment of relatedness will be made separately with respect to ABT-493/ABT-530, SOF, and RBV. The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

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 causality or deemed it as 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, "Other" cause of event must be provided by the investigator for the serious adverse event.

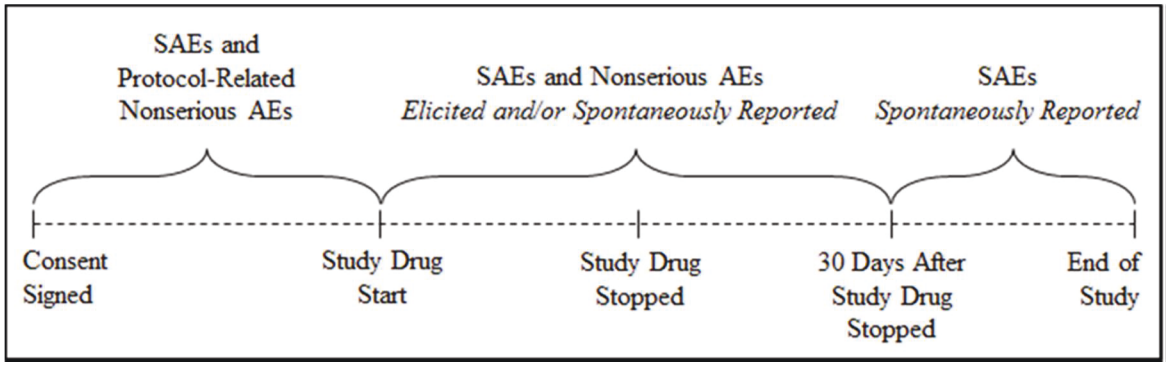
6.1.4 Adverse Event Collection Period

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 the administration of the first dose of study drug. From the time of the administration of the first dose of study drug until 30 days following discontinuation of study treatment, all adverse events and serious 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 should be faxed to Clinical Pharmacovigilance within 24 hours of the site becoming aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Antiviral Safety Team at:

Antiviral Safety Team
Dept. R48S, Bldg. AP30-3
1 North Waukegan Road
North Chicago, IL 60064

Office: (847) 938-1870
Email: SafetyManagement_Virology@abbvie.com

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

Therapeutic Area Medical Director:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:
Office:
Mobile:
eFAX:
Email: [redacted]

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: +1 (973) 784-6402

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Global and Local Regulations. The reference document used for SUSAR reporting will be the most current version of the Investigator's Brochure. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Summary of Product Characteristics (SmPC).

6.1.6 Pregnancy

Subjects and their partners should avoid pregnancy, and males should avoid sperm donation, starting with Study Day 1 until 4 months for females subjects and 7 months for male subjects and their female partners after stopping RBV, or as directed by local RBV label, whichever is more restrictive.

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Follow Section 5.4.1 if a female subject has a positive pregnancy test during the Treatment Period. Subjects 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 through the duration of the study (or per local RBV label). The investigator is encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry. 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

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator. All adverse events and laboratory abnormalities will be managed and followed to a satisfactory clinical resolution. A toxicity is deemed "clinically significant" based on the medical judgment of the investigator. Please refer to Section 6.1.7.1, Section 6.1.7.2, Section 6.1.7.3, Section 6.1.7.4, Section 6.1.7.5, and Section 6.1.7.6 for details on Toxicity Grades.

Interruption of DAA therapy is not recommended, and if interruption occurs under extenuating circumstances (e.g., due to hospitalization of the subject), it should be less than 7 consecutive days. If study drug interruption lasts for longer than 7 days, the investigator should contact the AbbVie Study TA MD. The Investigator should ensure that any study drug interruptions or RBV dose modifications and associated adverse events are promptly entered into the appropriate eCRFs.

The toxicity management guidelines below should be followed throughout the Treatment Period of the study. Specific toxicity management guidelines apply to the instances of:

decreases in hemoglobin for subjects receiving RBV (Section 6.1.7.4), increases in ALT (Section 6.1.7.5), and reductions in Creatinine Clearance (Section 6.1.7.6).

6.1.7.1 Grade 1 or 2 Laboratory Abnormalities and/or Adverse Events

Subjects who develop Grade 1 or 2 laboratory abnormalities or adverse events may continue study drugs with appropriate medical management and follow-up per study protocol.

6.1.7.2 Grade 3 or 4 Laboratory Abnormalities

With the exception of Grade 3 or higher abnormalities of uric acid, phosphorus, total cholesterol, triglycerides, or glucose (in subjects with a history of diabetes), if a subject experiences a Grade 3 or greater laboratory abnormality during the treatment period, the abnormal laboratory test should be repeated (repeat testing should be done on a re-drawn sample). If the Grade 3 or greater abnormality is confirmed, the investigator should assess whether the abnormality can be managed medically as per local practice without interruption of study drug or whether study drugs should be interrupted and the laboratory parameter followed until it improves.

If study drugs are interrupted and restarted and the abnormality recurs, then study drugs should be permanently discontinued.

Decreases in hemoglobin level should be managed according to the guidance in Section 6.1.7.4, elevations of serum ALT should be managed according to the guidance in Section 6.1.7.5 and reductions in creatinine clearance for subjects receiving RBV should be managed according to the guidance in Section 6.1.7.6. Grade 3 or greater abnormalities of uric acid, phosphorus, 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, unless deemed necessary by the investigator.

6.1.7.3 Grade 3 or 4 Adverse Events or Serious Adverse Events

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 investigator should assess whether the adverse event can be managed medically without interruption of study drug, or whether study drugs should be interrupted until it improves.

If study drugs are interrupted and restarted and the adverse event recurs, then study drugs should be permanently discontinued.

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, it is not necessary to interrupt study drugs unless an interruption is required because of the nature of the event (e.g., unable to take oral medications).

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 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 Receiving RBV

Reductions in hemoglobin are a well characterized side effect of RBV exposure. If a subject experiences a hemoglobin decrease that meets the criteria outlined in Table 13, a confirmatory test should be performed. If the hemoglobin decrease is confirmed to meet the criteria, the management guidelines in Table 13 should be followed, unless local RBV label requires a more stringent management. Management will be different for subjects without a history of known cardiac disease and subjects with known cardiac disease.

Use of hematologic growth factors (such as erythropoietin, filgrastim), or blood transfusions is not recommended and is permitted only with approval of the AbbVie Study TA MD. 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 requires approval of the AbbVie Study TA MD, except for more stringent management requirement from a local RBV label.

Table 13. Management of Hemoglobin Decreases

Hemoglobin Reduction in Patients Without Cardiac Disease or History of Cardiac Disease	
Hemoglobin < 10.0 g/dL, but ≥ 8.5 g/dL	Study drugs may be continued
	Reduce RBV dose to 600 mg QD* and continue to monitor hemoglobin levels per protocol
	If hemoglobin increases to ≥ 10 g/dL, may increase RBV, with gradual dose increases in 200 mg increments towards original dose
	If Hb decreases to < 8.5 g/dL see appropriate row below
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event
Hemoglobin < 8.5 g/dL	Permanently discontinue RBV and manage the subject as medically appropriate
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event
Reduction in Patients with Stable Cardiac Disease or History of Stable Cardiac Disease	
Hemoglobin decrease of ≥ 2 g/dL during a 4-week treatment period (Hemoglobin ≥ 10 g/dL)	Study drugs may be continued
	Reduce RBV dose to 600 mg QD* and continue to monitor hemoglobin levels per protocol
	If a subsequent hemoglobin result is greater than the level that triggered the dose reduction, the investigator may elect to increase RBV, with gradual, 200 mg dose increases towards the original dose
	If the subject has symptoms consistent with their cardiac disease, manage subject as medically appropriate and AbbVie Study TA MD may be contacted
	If hemoglobin does not increase, investigator may manage the subject as medically appropriate. If hemoglobin decreases to < 10 g/dL see appropriate row below
Hemoglobin < 10.0 g/dL, but ≥ 8.5 g/dL	Study drugs may be continued
	Continue at reduced RBV dose as above (or reduce RBV dose to 600 mg QD* if this is the initial reduction) and continue to monitor hemoglobin per protocol
	If hemoglobin increases to ≥ 10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose
	If hemoglobin < 10 g/dL despite being for 4 weeks on the reduced RBV dose, permanently discontinue RBV and manage the subject as medically appropriate
Hemoglobin < 8.5 g/dL or < 12 g/dL after 4 weeks of dose reduction	Permanently discontinue RBV and manage the subject as medically appropriate
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event

* For subjects aged 12 to less than 18, RBV dose reduction should be per local RBV label.

Management of other hematologic parameters besides hemoglobin (like WBC, platelets, neutrophils, etc.) should be performed according to the local RBV label. Alternative RBV dosing can be used if agreed upon by AbbVie TA MD.

6.1.7.5 Management of Increases in ALT

If a subject experiences a post-baseline ALT value ≥ 5 × ULN that is also ≥ 2 × Baseline value, the subject should have a confirmatory test should be performed. If, the ALT is value confirmed ≥ 5 × ULN, and ≥ 2 × Baseline value, the recommendations below should be followed:

- Complete hepatic questionnaire
- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain Anti-HAV IgM, Anti-HAV Total, Anti-HBc IgM, Anti-HBc Total, Anti-HBs, HBV DNA, HBsAg, Anti-HEV IgM, Anti-HEV IgG and HEV RNA, and other additional tests, as appropriate.
- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs if any of the following is observed at any time:
  - ALT level is ≥ 20 × ULN in the absence of an alternate etiology.
  - Increasing direct bilirubin or INR or onset of symptoms/signs of hepatitis.
  - At the discretion of the investigator.

Alternate management of confirmed ALT increases requires approval of the AbbVie Study TA MD.

6.1.7.6 Management of Reductions in Creatinine Clearance for Subjects Receiving RBV

Estimated glomerular filtration rate (eGFR, calculated using the MDRD equation) and Creatinine clearance (CrCl, estimated using the Cockcroft-Gault equation) will be calculated throughout the study. Both results will be provided to the investigators, but toxicity management and RBV dose adjustment will be performed based on CrCl values only.

If a subject experiences an CrCl value below 50 mL/min, a confirmatory test should be performed as soon as possible. If CrCl is confirmed to be below 50 mL/min, medical evaluation should include a full review of concurrent medications, including those taken on an as needed basis, those which are sold over the counter, and any dietary and herbal supplements.

In addition, the following should occur:

- Concomitant medication dose reduction based on CrCl or eGFR should be done as per local prescribing information of the concomitant medication (if applicable).
- The AbbVie Study TA MD should be contacted to discuss whether dose modification or drug substitution may be required for concomitant medications given the reduced kidney function as well as potential drug interactions with the DAAs. Drug interactions between concomitant medications and the DAAs, for example, could potentially increase antihypertensive medications' exposures, especially in the setting of reduced kidney function and may result in further deterioration of renal function. Also, if anti-hypertensive medications are adjusted, vital signs must be closely monitored to ensure appropriate blood pressure control.
- The dose of RBV should be adjusted as follows:
  - for CrCl between 30 and 50 mL/min: alternating doses of 200 and 400 mg every other day;
  - for CrCl less than 30 mL/min – 200 mg daily.
- A urine specimen should be obtained for urinalysis (including urine for albumin), and a separate urine specimen for archive should be obtained.
- Creatinine clearance and any other necessary analytes should be repeated within 7 days and as clinically indicated until resolution.
  - If CrCl improves to > 50 mL/min within 14 days after RBV dose modification, consideration should be given to increase RBV dose towards the original value. If CrCl decreases below 50 mL/min again, RBV should be permanently discontinued.

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

Alternative management of RBV dose in the setting of reduced renal function will require approval of the AbbVie Study TA MD, unless it is a more stringent management required by local RBV label.

6.1.8 Collection of Data Regarding Known AIDS-Defining Conditions

HIV-1 infected subjects participating in clinical trials may develop conditions typically associated with AIDS. A list of these known AIDS-Defining Conditions (ADCs) is presented in Appendix D. The events listed in Appendix D will be summarized as HIV-related events, not as adverse events. These ADCs will be collected from the time of study drug administration until 30 days following discontinuation of study drug.

6.2 Product Complaint

6.2.1 Definition

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

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 1 business day 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), and the following AbbVie Clinical Monitors:

Primary Contact:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Cell:
Email: [redacted]

Alternate Contact:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Cell:
Fax:
Email: [redacted]

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will occur after all subjects have completed the PT Week 12 Visit or prematurely discontinued the study. The data for the primary analysis will be locked after 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. An interim analysis may be conducted for the purpose of regulatory interaction.

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

Safety, and demographic analyses will be performed on all subjects who receive at least one dose of study drug. Analyses, as specified in the statistical analysis plan, will be presented by treatment arm and overall. Efficacy analyses will be performed on the intent-to-treat (ITT) population defined as all enrolled subjects who receive at least one dose of study drug, unless otherwise specified. Sensitivity analyses of the primary efficacy endpoint, when applicable, will be performed on the intention-to-treat population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-VF).

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

8.1.1 Demographics

Demographics and baseline characteristics will be summarized for all treated subjects by treatment arm and overall. Demographics include age, weight, height, waist circumference, 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, DAA regimen received in prior AbbVie HCV study, treatment experience prior to enrolling in the AbbVie HCV parent study, baseline RAVs prior to entering the current re-treatment study, other previous HCV regimens, HCV genotype, baseline HCV RNA levels, baseline fibrosis stage (F0 – F1, F2, F3, F4), 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, history of cardiovascular disease, and geographic region.

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

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

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. 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.

8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the percentage of subjects in the ITT population who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug), by treatment arm and overall. The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of virologic failures is less than 5, then the Wilson's score method will be used for the confidence interval instead.

A summary of reason for SVR_{12} non-response (e.g., OTVF, relapse, other) will be provided.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The percentage of subjects with HCV on treatment virologic failure by treatment arm and overall;
- The percentage of subjects with post-treatment HCV virologic relapse by treatment arm and overall. Subjects with reinfection will be summarized separately.

For the analysis of HCV virologic relapse, completion of treatment is defined as any subject with study drug duration of 77 days and 103 days or greater for subjects allocated to treatment durations of 12 weeks and 16 weeks, respectively.

For each treatment arm and overall, as applicable, the number and percentage of subjects meeting each secondary efficacy endpoint will be summarized along with a two-sided 95% confidence interval using Wilson's score method.

8.1.2.3 Sensitivity Analysis

The two-sided 95% confidence interval using Wilson's score method will also be calculated as a sensitivity analysis for the primary endpoint of SVR_{12} based on ITT population.

As sensitivity analyses, the number and percentage of subjects in the mITT-VF populations achieving SVR_{12}, as applicable, will be summarized along with a two-sided 95% confidence interval using Wilson's score interval and the Normal approximation to the binomial distribution by treatment arm and overall.

8.1.2.4 Subgroup Analysis

The summary statistics of subjects with SVR_{12} will be provided for the following subgroups:

- HCV genotype (1, 2, 3 4, 5, or 6);

- DAA-containing regimen received in the AbbVie HCV parent study:
  - ABT-493/ABT-530
  - 3D or 2D
- Previous treatment experience prior to enrolling in the AbbVie HCV parent study:
  - Treatment naive
  - Treatment experienced, DAA-naïve
  - Treatment experienced, PI-experienced only
  - Treatment experienced, NS5Ai-experienced only
  - Treatment experienced, PI- and NS5Ai-experienced
  - Treatment experienced, NS5Bi-experienced only
  - Treatment experienced, NS5Bi- and PI-experienced
  - Treatment experienced, NS5Bi- and NS5Ai-experienced
  - Treatment experienced, NS5Bi-, PI- and NS5Ai-experienced
- Baseline RAVs prior to entering the current re-treatment study: NS3A alone, NS5A alone, NS5B alone, NS3A and NS5A, NS3A and NS5B, NS5A and NS5B, NS3A and NS5A and NS5B;
- Baseline fibrosis stage (F0 – F1, F2, F3, or F4);
- Baseline HCV RNA level (< 6,000,000 or ≥ 6,000,000 IU/mL) and (< 2,000,000, ≥ 2,000,000 to < 6,000,000, ≥ 6,000,000 to < 10,000,000, or ≥ 10,000,000 IU/mL);

For subjects with cirrhosis only:

- Baseline Child-Pugh Score (5, 6, or > 6);
- Baseline APRI (≤ 2 or > 2);
- Baseline platelets (< 90 or ≥ 90 × 10^9/L; < 50 or ≥ 50 × 10^9/L; < 100 or ≥ 100 × 10^9/L; < 150 or ≥ 150 × 10^9/L);
- Baseline albumin (< 35 or ≥ 35 g/L);
- Any of baseline platelets < 90 × 10^9/L and baseline albumin < 35 g/L;

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 by treatment arm and overall:

- 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 who achieve SVR 4 weeks after the last actual dose of study drug (SVR_4);
- The percentage of subjects who achieve SVR 24 weeks after the last actual dose of study drug (SVR_{24});
- The percentage of subjects who relapse after achieving SVR_{12}.

The number and percentage of subjects meeting each additional efficacy endpoint will be summarized along with a two-sided 95% confidence interval using the Wilson's score interval.

8.1.3 HCV Resistance Analyses

The genes of interest for NGS in this study are those encoding full length NS3/4A, NS5A and NS5B. For each DAA target, signature resistance-associated amino acid positions will be identified by AbbVie Clinical Virology. An appropriate prototypic reference sequence will be used for comparison with sequences from samples.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of HCV virologic failure or treatment discontinuation is < 1000 IU/mL, the sample closest in time after HCV virologic failure/treatment discontinuation with an HCV RNA level ≥ 1000 IU/mL will be used. Included time points for analyses on samples from subjects who do not achieve SVR_{12} are 1) the sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1000 IU/mL,

and 2) 24 weeks post-DAA treatment, provided that resistance-associated variants were detected by NGS at the time of HCV virologic failure/treatment discontinuation.

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

- Baseline variant: a variant (by NGS) in a baseline sample (≥ 2% or ≥ 15% prevalence within a subject's viral population depending on variant frequency threshold utilized) that was not present in 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 (< 2%) in the subject and is detectable in ≥ 2% of the sequences from the post-baseline sample in a given DAA target.
- Enriched variant: variant present in both the baseline and a post-baseline sample whose prevalence in the post-baseline sample is at least 20 percentage points greater than the prevalence in the baseline sample [(post-baseline % – baseline %) ≥ 20]
- Treatment-emergent variant: A post-baseline variant or an enriched variant.
- Variant at signature amino acid position: variant (relative to reference) present in a baseline or a post-baseline sample at a signature amino acid position.

The following analyses will be performed for all subjects:

To characterize prior HCV DAA resistance patterns in the study population, available resistance analysis data obtained at the time of the subject's virologic failure of the previous DAA treatment will be collected and reported.

For all subjects, the following will be provided:

- The number and percentage of subjects with baseline variants at detection-thresholds of ≥ 2% and ≥ 15% for variants at signature amino acid positions, and ≥ 15% for variants at non-signature positions.
- A listing of all baseline variants (≥ 2% detection threshold) at signature resistance-associated amino acid positions for each DAA target.

- A listing of all baseline variants (≥ 15% detection threshold) at non-signature resistance-associated amino acid positions for each DAA target.
- A listing of subjects with multiple baseline variants at signature amino acid positions (each at ≥ 15% prevalence within a subject's viral population), either within a DAA target or across any 3 DAA targets.
- The impact of baseline variants on treatment outcome will be assessed as follows: for each variant, the SVR_{12} rate will be calculated for subjects with and without the variant and the 2 rates will be compared. Analyses will be grouped by subject's HCV subtype and DAA target. Subjects not achieving SVR_{12} due to non-virologic reasons will be excluded from this analysis. These analyses will be performed based on the following criteria:
  - An analysis will be performed based on amino acid position, using detection thresholds of ≥ 2% and ≥ 15% for all variants at each signature amino acid position and a detection threshold of ≥ 15% for all variants at each non-signature amino acid position.
  - An additional analysis will be performed using detection thresholds of ≥ 2% and ≥ 15% for the impact of each specific variant as specified by clinical virology.

The following will be provided for subjects who do not achieve SVR_{12} and have post-baseline resistance data available:

- A listing by subject of all treatment-emergent variants relative to the baseline sequence will be provided for each DAA target
- A listing by subject of all variants at signature amino acid positions
- The number and percentage of subjects (with subject listing) with variants emerging at an amino acid position relative to baseline
- The number and percentage of subjects (with subject listing) with certain specific emerged variants

The persistence of post-baseline variants at signature resistance-associated amino acid positions for each target will be assessed by NGS at Post-Treatment Week 24. A listing

by subject and time point of all post-baseline variants relative to the baseline amino acid sequence will be provided for each DAA target.

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

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

8.1.4 HIV Resistance Analyses

If a subject develops a confirmed, plasma HIV-1 RNA level ≥ 500 copies/mL after starting the study, the subject's HIV-1 PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays. The number of subjects who demonstrate HIV genotypic resistance and the genotypic resistant mutations detected in the samples obtained from these subjects will be tabulated and summarized. Resistance will be defined as described by the IAS-USA Panel.[48]

8.1.5 Safety

All subjects who receive at least one dose of study drug will be included in the safety analyses. All safety analysis will be done by treatment arm and overall.

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 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). The tabulation of the number of subjects with treatment-emergent adverse events by severity grade (Grades 1 – 5) and relationship

to each 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.

Additional analyses will be described in the statistical analysis plan.

8.1.5.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized 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 descriptively.

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 percentage of subjects who experience post-baseline shifts during treatment in clinical laboratory values from low/normal to high and high/normal to low based on the normal range will be summarized.

In addition, the number and percentage of subjects with post-baseline values meeting pre-specified criteria for Potentially Clinically Significant laboratory values or toxicity grades during treatment will be summarized.

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. The number and percentage of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant vital signs values during treatment will be summarized.

8.1.5.4 HCV/HIV-1 Co-Infection

The following additional safety data will be summarized and analyzed for subjects with HCV/HIV-1 co-infection overall and in each treatment arm:

- The percentage of subjects with plasma HIV-1 RNA suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm;
- The number and percentage of subjects with plasma HIV-1 RNA < 20 copies/mL at each applicable time point;
- Change from baseline in CD4+ T-cell count (absolute and percent) to each applicable post-baseline time point;
- Change from baseline in lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) to each applicable post-baseline time point;
- The listing of subjects with a plasma HIV-1 RNA value ≥ 200 copies/mL at any baseline or post-baseline visit during the study.

The analysis of change from baseline in CD4+ T-cell count (absolute and percent), lymphocytes (count and percentage) and CD8+ T-cell counts (absolute and percent) will report the mean and median values at baseline and at each applicable post-baseline visit, as well as N, mean, median, standard deviation (SD), minimum and maximum values for the change from baseline overall and within each treatment arm.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of ABT-530, ABT-493, RBV, SOF and GS-331007 and pharmacokinetic parameter values for ABT-493 and ABT-530 will be tabulated for each subject and group. Summary statistics will be computed for each time and visit.

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

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (version VII, or higher version). The

structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent volume of distribution (V/F) of the PK analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. The evaluation criteria described below will be used to examine the performance of different models.

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

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using stepwise forward selection method, or a 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 i1, 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 (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 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.

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

8.2 Determination of Sample Size

It is anticipated that approximately 50 HCV infected, DAA treatment-experienced subjects who have experienced virologic failure in an AbbVie HCV parent study will be enrolled.

8.3 Randomization Methods

This study is not randomized. Eligible subjects will be allocated to a treatment arm according to their HCV genotype, cirrhosis status (presence/absence), and prior treatment experience with PI- and/or NS5Ai-containing regimens before experiencing virologic failure in the AbbVie HCV parent study.

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 and approval by Regulatory Authority(ies), if required by local regulations, 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 and all other applicable regulatory authorities.

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 Council on Harmonisation (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.

The optional pharmacogenetic testing and analyses will only be performed if the subject has voluntarily signed and dated the IRB/IEC approved pharmacogenetic informed consent, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the additional pharmacogenetic testing, it will not impact the subject's participation in the study.

In the event a subject withdraws from the main study, optional pharmacogenetic exploratory research samples will continue to be stored and analyzed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the subject must inform their study doctor, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

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 Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

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 will be 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

To ensure data integrity and subject safety, a study monitor will continuously, throughout the study, verify that all subjects sign the informed consent prior to any study specific procedures being conducted, that the protocol procedures are being followed appropriately, and that the information provided in the eCRF is complete, accurate, and supported by information in source documents. 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 pharmacogenetic exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be

informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional pharmacogenetic exploratory research may be provided to investigators and used in scientific publications or presented at medical conventions. Optional pharmacogenetic exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for Glecaprevir/Pibrentasvir, and the product labeling for SOF and RBV.
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:	An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Combination with Sofosbuvir and Ribavirin in Chronic Hepatitis C (HCV) Infected Subjects Who Have Experienced Virologic Failure in AbbVie HCV Clinical Studies (MAGELLAN-3)
Protocol Date:	06 November 2017

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

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

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

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not making 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
		Pharmacokinetics
		Clinical
		Statistics
		Clinical
		Bioanalysis

Appendix C. Study Activities

Study Activities – Treatment Period

Activity	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 (Arm B Only)	EOT/Premature D/C from Treatment[b]
Informed Consent[c]	X						
Medical History	X	X					
Physical Exam	X	X					X
Vital Signs, Weight, Waist Circumference, Height[d]	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])[e]	X (s, u)	X (s, u)		X (u)	X (u)	X (u)	X (u)
FSH (all females)	X						
HBsAg, Anti-HIV Ab	X						
Hemoglobin A1c	X						
HCV Genotype and Subgenotype	X						
FibroTest/APRI or FibroScan® or Liver Biopsy[f]	X						
Total Insulin		X					X
Concomitant Medication Assessment	X	X	X	X	X	X	X
Adverse Event Assessment[g]	X	X	X	X	X	X	X
Study Drugs Dispensed		X		X	X	X	

Activity	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 (Arm B Only)	EOT/Premature D/C from Treatment[b]
Study Drug Accountability and for Compliance			X	X	X	X	X
Dispense/Review Study Drug Dosing Card		X (Dispense only)	X	X	X	X	X (Review only)
HCV RNA Samples	X	X	X	X	X	X	X
HCV Resistance Sample		X	X	X	X	X	X
Archive Serum and Plasma Sample	X	X	X	X	X	X	X
Pharmacokinetic Samples[h]			X	X	X	X	X
Optional Pharmacogenetic Samples		X					
Child-Pugh Score[i]	X						X
Clinical Assessment of Hepatic Decompensation[i]		X					
HCC Screening: Liver Ultrasound[i]	X						
HIV-1 RNA[j]	X	X	X	X	X	X	X
Flow cytometry sample[j]	X	X				X	X

Wk = Week; EOT = End of treatment; D/C = Discontinuation

a. All procedures to be performed prior to first dose.

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

c. Subjects need to sign an IRB/IEC approved informed consent for the study (prior to performing any screening or study-specific procedures) and the optional pharmacogenetic sample(s), if applicable.

d. 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.

e. Females not of CBP at Screening do not require pregnancy testing (Section 5.2.4).

f. For subjects who were categorized as non-cirrhotic in the AbbVie parent study and have not had a qualifying liver biopsy within the previous 12 months or a qualifying FibroScan within the previous 6 months.

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

h. PK samples will be collected at each scheduled study visit except Day 1. Detail regarding timing of samples is provided in Section 5.3.2.1.

i. Child-Pugh Score, Clinical Assessment of Hepatic Decompensation and Liver Ultrasound are only performed for subjects with compensated cirrhosis as described in Section 5.3.1.1.

j. For HCV/HIV-1 co-infected subjects.

Study Activities – Post-Treatment (PT) Period

Activity	PT Wk 4	PT Wk 12	PT Wk 24 or PT D/C[a]
Vital Signs and Weight	X		
Hematology/Chemistry/Urinalysis/Coagulation Panel	X	X[b]	X[b,c]
Monthly Pregnancy Test (females)[d]	X (u)	X (u) (PT Weeks 8, 12, 16)	X (u)[c]
Concomitant Medication Assessment[e]	X	X	X
Adverse Event Assessment[f]	X	X	X
HCV RNA Samples	X	X	X
HCV Resistance Sample	X	X	X
Archive Serum and Plasma Sample	X	X	X
Optional Pharmacogenetic samples		X	
Child-Pugh Score[g]		X	X
HCC Screening: Liver Ultrasound[g]			X
HIV-1 RNA[h]	X	X	
Flow cytometry sample[h]	X	X	

Wk = Week; PT = Post-Treatment; D/C = Discontinuation

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

b. For the subjects enrolled with cirrhosis at Day 1. Chemistry and Coagulation Panel are required to calculate the Child Pugh Score.

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

d. Females not of CBP at Screening do not require pregnancy testing. Pregnancy testing should be completed every 4 weeks for 4 months after the last dose of RBV (or as directed per the local RBV label, whichever is more restrictive). At PT Weeks 8 and 16 subjects may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site. Additional testing may be required per local RBV label.

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

f. Nonserious AEs and all SAEs will be collected until 30 days post dosing. Only SAEs will be collected thereafter, see Section 6.1.4.

g. Required only for subjects with compensated cirrhosis as described in Section 5.3.1.1.

h. For subjects with HCV/HIV-1 co-infected subjects.

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

Appendix D. List of AIDS-Defining Conditions

Collection of data regarding known AIDS-Defining Conditions (ADCs) is covered in Section 6.1.8.

AIDS-Defining Conditions:

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age > 1 month
- Cytomegalovirus retinitis (with loss of vision)†
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary†
- Mycobacterium tuberculosis of any site, pulmonary,†§ disseminated,† or extrapulmonary†

- Mycobacterium, other species or unidentified species, disseminated† or extrapulmonary†
- Pneumocystis jirovecii pneumonia†
- Pneumonia, recurrent†§
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age > 1 month†
- Wasting syndrome attributed to HIV

* Only among children aged < 13 years.

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged > 13 years.

Cross reference: Morbidity and Mortality Weekly Report (MMWR). AIDS Defining Conditions. 2008. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2 htm.

Appendix E. Protocol Amendment: List of Changes

The summary of changes can be found in Section 1.1.

Specific Protocol Changes

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

Sponsor/Emergency Contact:	Therapeutic Area Scientific Director [redacted] 1 North Waukegan Road North Chicago, IL 60064 Phone: Cell: eFax: [redacted]	Therapeutic Area Medical Director [redacted] 1 North Waukegan Road North Chicago, IL 60064 Phone: eFax: [redacted]

Has been changed to read:

Sponsor/Emergency Contact:	Therapeutic Area Scientific Director [redacted] 1 North Waukegan Road North Chicago, IL 60064 Office: Mobile: eFax: [redacted]	Therapeutic Area Medical Director [redacted] 1 North Waukegan Road North Chicago, IL 60064 Office: Mobile: eFax: [redacted] Emergency 24 hour Number: +1 973-784-6402

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M15-942
Name of Study Drug: ABT-493/ABT-530, sofosbuvir (SOF), ribavirin (RBV)	**Phase of Development:** 3b
Name of Active Ingredient: ABT-493/ABT-530, SOF, RBV	**Date of Protocol Synopsis:** 19 October 2017
Protocol Title: An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Combination with Sofosbuvir and Ribavirin in Chronic Hepatitis C (HCV) Infected Subjects Who Have Experienced Virologic Failure in AbbVie HCV Clinical Studies (MAGELLAN-3)	
Objectives: • The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving a 12-week post-treatment sustained virologic failure response (SVR_{12}) in each treatment arm and safety of ABT-493/ABT-530 plus SOF and RBV in adults with chronic HCV GT1-6 infection who previously failed HCV treatment in an AbbVie HCV clinical study, designated as an AbbVie HCV parent study. • Secondary objectives are to assess the percentage of subjects with HCV on-treatment virologic failure, and the percentage of subjects with HCV virologic relapse.	
Investigators: Multicenter; investigator information on file at AbbVie	
Study Sites: Approximately 40 sites who participated in an AbbVie HCV parent study.	
Study Population: Subjects who have experienced virologic failure after receiving regimens containing ABT-493/ABT-530 in an AbbVie HCV parent study. Subjects who have experienced virologic failure during or after receiving ombitasvir/paritaprevir/r + dasabuvir (3D), ombitasvir/paritaprevir/r (2D) in AbbVie HCV parent study may be enrolled at AbbVie's discretion.	
Number of Subjects to be Enrolled: Approximately 50 subjects.	

Methodology:

This is a Phase 3b, open-label, non-randomized, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in combination with SOF and RBV in HCV GT1 – 6-infected subjects who have experienced virologic failure while participating in an AbbVie HCV parent study. Approximately 50 subjects will be enrolled. Treatment arm allocation will be based on HCV genotype, cirrhosis status, and treatment experience with protease inhibitor (PI) and/or NS5A inhibitor (NS5Ai)-containing regimens prior to enrolling in the AbbVie HCV parent study.

Treatment Arm Allocation in Study M15-942

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

* NC = non-cirrhotic; C = cirrhotic

** Subjects with mixed HCV genotype will be allocated to the longer treatment duration based on genotypes.

- Arm A: ABT-493/ABT-530 300/120 mg QD + SOF 400 mg QD + RBV 1000 – 1200 mg (weight-based) BID for 12 weeks
- Arm B: ABT-493/ABT-530 300/120 mg QD + SOF 400 mg QD + RBV 1000 – 1200 mg (weight-based) BID for 16 weeks

Arm A will enroll approximately 5 subjects, and Arm B will enroll approximately 45 subjects. All subjects administered at least one dose of study drugs will be followed for 24 weeks in the Post-Treatment Period to monitor HCV RNA and to evaluate efficacy and the emergence and/or persistence of resistance-associated viral variants.

Planned visits in the Treatment Period consist of Day 1, Weeks 2, 4, 8, and 12 for all subjects and an additional Week 16 visit for subjects in Arm B. During the Post-Treatment Period, subjects will have visits at Post-Treatment Weeks 4, 12, and 24. Efficacy and safety data will be monitored throughout the study. As this is an open-label study, safety will be reviewed by AbbVie.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female subjects (12 years of age and older, and weighing at least 45 kg), who experienced virologic failure during or after treatment with ABT-493/ABT-530 in an AbbVie HCV parent study. Subjects who have experienced virologic failure during or after receiving ombitasvir/paritaprevir/r + dasabuvir (3D), ombitasvir/paritaprevir/r (2D) in AbbVie HCV parent study may be enrolled at AbbVie's discretion.
2. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
3. Cirrhotic Subjects must have compensated cirrhosis, (Child-Pugh score of ≤ 6) at Screening and no current or past evidence of Child-Pugh B or C Classification or no clinical history of liver decompensation, including ascites noted on physical exam, hepatic encephalopathy or esophageal variceal bleeding.
4. Cirrhotic Subjects must have absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound (US), computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative US at Screening.

Main Exclusion:

1. History of severe, life-threatening or other clinically significant sensitivity to any study drug or drug component.
2. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for 4 months after the last dose of study drug, or as directed per the local RBV label.
3. 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, and failure in an AbbVie HCV parent study due to non-virologic reasons.
4. Positive test result at Screening for hepatitis B surface antigen (HBsAg).
5. Screening laboratory analyses showing creatinine clearance < 30 mL/min.
6. Discontinuation from the AbbVie HCV parent study for reasons other than virologic failure (e.g., non-adherence, lost to follow-up, and/or the occurrence of an adverse event).
7. Receipt of any HCV treatment after failing the treatment regimen in the AbbVie HCV parent study.

Investigational Products:	ABT-493/ABT-530 mg 100 mg/40 mg Film-coated Tablet Sofosbuvir 400 mg Film-coated Tablet Ribavirin 200 mg Film-coated Tablet
Doses:	ABT-493/ABT-530: 300 mg/120 mg QD (3 tablets) Sofosbuvir: 400 mg QD (1 tablet) Ribavirin: weight-based 1000 mg or 1200 mg per day in two divided doses (5 or 6 tablets)
Mode of Administration:	Oral with food
Reference Therapy:	N/A
Dose:	N/A
Mode of Administration:	N/A

Duration of Treatment: 12 or 16 weeks.

Criteria for Evaluation:

Efficacy:

Efficacy will be assessed utilizing plasma HCV RNA levels throughout the study.

Resistance:

The following information will be tabulated and summarized: 1) for all subjects receiving study drug 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 who do not achieve SVR_{12} and who have a post-baseline sample, all treatment-emergent variants relative to baseline.

Pharmacokinetic:

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

Safety:

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

Statistical Methods:

Efficacy:

The primary efficacy endpoint is the percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm and overall. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless number of virologic failures is less than 5, then the Wilson's score method will be used for the confidence interval instead.

The secondary efficacy variables are:

- The percentage of subjects with on-treatment HCV virologic failure in each treatment arm and overall;
- The percentage of subjects with post-treatment HCV virologic relapse in each treatment arm and overall.

The number and percentage of subjects meeting each secondary efficacy endpoint will be summarized along with a two-sided 95% confidence interval using the Wilson score method. Analyses of additional efficacy endpoints and efficacy subgroup analyses will be performed.

Resistance:

For all subjects receiving study drugs and with available samples, the variants at signature resistance-associated amino acid positions at baseline identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

The following resistance information will be analyzed for subjects receiving study drugs 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 NGS and comparison to the baseline sequence, 2) the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral variants by NGS.

Statistical Methods (Continued):

Pharmacokinetic:

Plasma concentrations of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), and RBV will be tabulated for each subject and treatment arm. Summary statistics will be computed for each treatment arm.

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). Safety summaries will be provided by treatment arm and overall. 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 MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug. Change from baseline in laboratory tests and vital signs measurements to each time point of collection will be summarized, and values that are potentially clinically significant, according to predefined criteria, will be summarized by treatment arm and overall.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M15-942
Name of Study Drug: ABT-493/ABT-530, sofosbuvir (SOF), ribavirin (RBV)	**Phase of Development:** 3b
Name of Active Ingredient: ABT-493/ABT-530, SOF, RBV	**Date of Protocol Synopsis:** 06 November 2017
Protocol Title: An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Combination with Sofosbuvir and Ribavirin in Chronic Hepatitis C (HCV) Infected Subjects Who Have Experienced Virologic Failure in AbbVie HCV Clinical Studies (MAGELLAN-3)	
Objectives: • The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving a 12-week post-treatment sustained virologic failure response (SVR_{12}) in each treatment arm and safety of ABT-493/ABT-530 plus SOF and RBV in adults or adolescents with chronic HCV GT1-6 infection who previously failed HCV treatment in an AbbVie HCV clinical study, designated as an AbbVie HCV parent study. • Secondary objectives are to assess the percentage of subjects with HCV on-treatment virologic failure, and the percentage of subjects with HCV virologic relapse.	
Investigators: Multicenter; investigator information on file at AbbVie	
Study Sites: Approximately 40 sites who participated in an AbbVie HCV parent study.	
Study Population: Subjects who have experienced virologic failure after receiving regimens containing ABT-493/ABT-530 in an AbbVie HCV parent study. Subjects who have experienced virologic failure during or after receiving ombitasvir/paritaprevir/r + dasabuvir (3D), ombitasvir/paritaprevir/r (2D) in an AbbVie HCV parent study may be enrolled at AbbVie's discretion.	
Number of Subjects to be Enrolled: Approximately 50 subjects.	

Methodology:

This is a Phase 3b, open-label, non-randomized, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in combination with SOF and RBV in HCV GT1 – 6-infected subjects including subjects with compensated cirrhosis and/or HIV-1 coinfection who have experienced virologic failure while participating in an AbbVie HCV parent study. Approximately 50 subjects will be enrolled. Treatment arm allocation will be based on HCV genotype, cirrhosis status, and treatment experience with protease inhibitor (PI) and/or NS5A inhibitor (NS5Ai)-containing regimens prior to enrolling in the AbbVie HCV parent study.

Treatment Arm Allocation in Study M15-942

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

* NC = non-cirrhotic; C = cirrhotic

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

- Arm A: Subjects will receive orally ABT-493/ABT-530 300/120 mg QD, SOF 400 mg QD, RBV 600 mg to 1200 mg daily in two divided doses (based on baseline age and weight) for 12 weeks
- Arm B: Subjects will receive orally ABT-493/ABT-530 300/120 mg QD, SOF 400 mg QD, RBV 600 mg to 1200 mg daily in two divided doses (based on baseline age and weight) for 16 weeks

Arm A will enroll approximately 5 subjects, and Arm B will enroll approximately 45 subjects. All subjects administered at least one dose of study drugs will be followed for 24 weeks in the Post-Treatment Period to monitor HCV RNA and to evaluate efficacy and the emergence and/or persistence of resistance-associated viral variants.

Planned visits in the Treatment Period consist of Day 1, Weeks 2, 4, 8, and 12 for all subjects and an additional Week 16 visit for subjects in Arm B. During the Post-Treatment Period, subjects will have visits at Post-Treatment Weeks 4, 12, and 24. Efficacy and safety data will be monitored throughout the study. As this is an open-label study, safety will be reviewed by AbbVie.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female subjects must be adults (18 years of age or older) or adolescents (12 to less than 18 years of age weighing at least 35 kg).
2. Subject must have experienced virologic failure during or after treatment with ABT-493/ABT-530 in an AbbVie HCV parent study. Subjects who have experienced virologic failure during or after receiving ombitasvir/paritaprevir/r + dasabuvir (3D), or ombitasvir/paritaprevir/r (2D) in an AbbVie HCV parent study may be enrolled at AbbVie's discretion. Treatment in the parent study must have been completed or discontinued at least 1 month prior to the Screening Visit.
3. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
4. Cirrhotic Subjects must have compensated cirrhosis, (Child-Pugh score of ≤ 6) at Screening and no current or past evidence of Child-Pugh B or C Classification or no clinical history of liver decompensation, including ascites noted on physical exam, hepatic encephalopathy or esophageal variceal bleeding.
5. Cirrhotic Subjects must have absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound (US), computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative US at Screening.

Main Exclusion:

1. History of severe, life-threatening or other clinically significant sensitivity to any study drug or drug component.
2. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for 4 months after the last dose of study drug, or as directed per the local RBV label, whichever is more restrictive.
3. 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, and failure in an AbbVie HCV parent study due to non-virologic reasons.
4. Positive test result at Screening for hepatitis B surface antigen (HBsAg).
5. Screening laboratory analyses showing calculated creatinine clearance < 30 mL/min.
6. Discontinuation from the AbbVie HCV parent study for reasons other than virologic failure (e.g., non-adherence, lost to follow-up, and/or the occurrence of an adverse event).
7. Receipt of any HCV treatment after failing the treatment regimen in the AbbVie HCV parent study.

Investigational Products:	ABT-493/ABT-530 mg 100 mg/40 mg Film-coated Tablet Sofosbuvir 400 mg Film-coated Tablet Ribavirin 200 mg Film-coated Tablet
Doses:	ABT-493/ABT-530: 300 mg/120 mg QD (3 tablets) Sofosbuvir: 400 mg QD (1 tablet) Ribavirin: • For subjects aged 18 or more: 1000 mg or 1200 mg daily in two divided doses • For subjects 12 less than 18 years old: 600 mg to 1200 mg daily in two divided doses
Mode of Administration:	Oral with food
Reference Therapy:	N/A
Dose:	N/A
Mode of Administration:	N/A
Duration of Treatment: 12 or 16 weeks.	

Criteria for Evaluation:

Efficacy:

Efficacy will be assessed utilizing plasma HCV RNA levels throughout the study.

Resistance:

The following information will be tabulated and summarized: 1) for all subjects receiving study drug 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 who do not achieve SVR_{12} and who have a post-baseline sample, all treatment-emergent variants relative to baseline.

Pharmacokinetic:

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

Safety:

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

Statistical Methods:

Efficacy:

The primary efficacy endpoint is the percentage of subjects who achieve SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm and overall. The primary endpoint will be analyzed based on intention to treat (ITT) population. The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of virologic failures is less than 5, then the Wilson's score method will be used for the confidence interval instead.

The secondary efficacy variables are:

- The percentage of subjects with on-treatment HCV virologic failure in each treatment arm and overall;
- The percentage of subjects with post-treatment HCV virologic relapse in each treatment arm and overall.

The number and percentage of subjects meeting each secondary efficacy endpoint will be summarized along with a two-sided 95% confidence interval using the Wilson score method. Analyses of additional efficacy endpoints and efficacy subgroup analyses will be performed.

Resistance:

For all subjects receiving study drugs and with available samples, the variants at signature resistance-associated amino acid positions at baseline identified by next generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence will be analyzed.

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

Pharmacokinetic:

Plasma concentrations of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), and RBV will be tabulated for each subject and treatment arm. Summary statistics will be computed for each treatment arm.

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). Safety summaries will be provided by treatment arm and overall. 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 MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by grade and relationship to study drug. Change from baseline in laboratory tests and vital signs measurements to each time point of collection will be summarized, and values that are potentially clinically significant, according to predefined criteria, will be summarized by treatment arm and overall.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
"HIV-1," "CPB" and "PT" previously read:

HIV-1	Human immunodeficiency virus
CPB	Childbearing potential
PT	Post-Treatment

Has been changed to read:

HIV-1	Human immunodeficiency virus type 1
CBP	Childbearing potential
PT	Post-Treatment/preferred term

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add:

ADC	AIDS-Defining Conditions
HCC	Hepatocellular carcinoma
OTVF	On-treatment Virologic Failure
US	Ultrasound
CrCl	Creatinine clearance

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Delete:

sAFP	Serum Alpha-Fetoprotein
ASV	Asunaprevir
CPK	Creatine phosphokinase
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
GCSF	Granulocyte colony stimulating factor
HCV Ab	Hepatitis C virus antibody
LLN	Lower limit of normal
PCR	Polymerase Chain Reaction
QTc	QT interval corrected for heart rate
QTcF	QTc using Fridericia's correction formula
RT-PCR	Reverse transcriptase PCR
SOC	System Organ Class/Standard of Care

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Pharmacokinetic and Statistical Abbreviations
Previously read:

AUC	Area under the plasma concentration-time curve
AUC_{24}	AUC for the 24-hour dosing interval
β	Apparent terminal phase elimination rate constant
CL/F	Apparent oral plasma clearance
CR/CL	Creatinine clearance
C_{max}	Maximum observed plasma concentration
C_{trough}	Pre-dose trough plasma concentration
MAD	Multiple Ascending Dose
NONMEM	Non-linear mixed-effect modeling
PK	Pharmacokinetic
SAD	Single Ascending Dose
$t_{1/2}$	Terminal phase elimination half-life
T_{max}	Time to maximum observed plasma concentration (C_{max})
V/F	Apparent Volume of distribution

Has been changed to read:

AUC	Area under the plasma concentration-time curve
AUC_{0-24}	AUC for the 24-hour dosing interval
CL/F	Apparent oral plasma clearance
C_{max}	Maximum observed plasma concentration
NONMEM	Non-linear mixed-effect modeling
PK	Pharmacokinetic
T_{max}	Time to maximum observed plasma concentration (C_{max})
V/F	Apparent Volume of distribution

Section 3.0 Introduction
Third paragraph previously read:

The next generation DAA regimens with high potencies across all HCV genotypes and across patient subpopulations are under investigation, including AbbVie's next generation DAAs combination therapy, ABT-493/ABT-530, currently in Phase 3 clinical development.

Has been changed to read:

The next generation DAA regimens have high potencies across all HCV genotypes and across patient subpopulations, including Abbvie's ABT-493/ABT-530 or glecaprevir/pibrentasvir (GLE/PIB). GLE/PIB is approved in some parts of the world, including Europe and the United States, under the brand name MAVIRET® or MAVYRET™, respectively.

Table 1. In Vitro Antiviral Activity of ABT-493 and Other Protease Inhibitors Against HCV Genotypes 1, 2, 3, 4, and 6
Row "ABT-493" previously read:

	Stable HCV Replicon EC_{50} (nM)					
Protease Inhibitor	**GT1a**	**GT1b**	**GT2a**	**GT3a**	**GT4a**	**GT6a**
ABT-493	0.85	0.94	2.7[a]	1.6	2.8	0.86

Has been changed to read:

	Stable HCV Replicon EC_{50} (nM)					
Protease Inhibitor	**GT1a**	**GT1b**	**GT2a**	**GT3a**	**GT4a**	**GT6a**
ABT-493	0.85	0.94	2.2[a]	1.9	2.8	0.86

Section 3.0 Introduction
Subsection ABT-493
Last paragraph, last sentence previously read:

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology and Phase I data can be found in the Investigator's Brochure.[13]

Has been changed to read:

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology and Phase I data can be found in the Investigator's Brochure.[13]

Section 3.0 Introduction
Subsection ABT-530
Last paragraph, last sentence previously read:

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology and Phase 1 data can be found in the Investigator's Brochure.[22]

Has been changed to read:

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology and Phase 1 data can be found in the Investigator's Brochure.[13]

Section 3.0 Introduction
Subsection HCV/HIV-1 Co-Infection
Last paragraph, last sentence previously read:

Per the most recent AASLD treatment guidelines, it is recommended that HCV/HIV-1 co-infected patients be treated and re-treated the same as HCV mono-infected patients, albeit with attention paid to potential drug-drug interactions with anti-retroviral medications.

Has been changed to read:

Per the most recent AASLD treatment guidelines, it is recommended that HCV/HIV-1 co-infected patients be treated and re-treated the same as HCV mono-infected patients, albeit with attention paid to potential drug-drug interactions with anti-retroviral medications.[31]

Section 3.0 Introduction
Subsection ARV Drug-Drug Interaction Studies with ABT-493 and ABT-530
Fifth paragraph, last sentence previously read:

Coadministration of ABT-493 + ABT-530 with ritonavir boosted atazanavir was studied in a DDI study that was terminated early due to an increase in ABT-493 exposure up to 16-fold and ABT-530 exposure up to 3-fold with Grade 1 and 2 increases in ALT and Grade 2 to 3 increase in total bilirubin (predominately indirect).

Has been changed to read:

Coadministration of ABT-493 + ABT-530 with ritonavir boosted atazanavir was studied in a DDI study that was terminated early due to an increase in ABT-493 exposure up to 16-fold and ABT-530 exposure up to 3-fold with Grade 1 and 2 increases in alanine aminotransferase (ALT) and Grade 2 to 3 increase in total bilirubin (predominately indirect).

Section 3.0 Introduction
Subsection ARV Drug-Drug Interaction Studies with ABT-493 and ABT-530
Sixth paragraph, first and second sentence previously read:

A recently completed study (Study M15-584) evaluating the drug interaction profile when ABT-493/ABT-530 300 mg/120 mg is co administered with Genvoya® (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir alafenamide10 mg QD), Study M15-584 has recently been completed. Coadministration was safe and well tolerated, with mild side effects reported and one grade 3 neutropenia deemed related to the combination of Genvoya, ABT-493 and ABT-530 in a black male subject with baseline low ANC, leading to premature study drug discontinuation.

Has been changed to read:

Study M15-584 evaluated the drug interaction profile when ABT-493/ABT-530 300 mg/120 mg is co-administered with Genvoya® (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir alafenamide10 mg QD). Co-administration was safe and well tolerated, with mild side effects reported and one grade 3 neutropenia deemed related to the combination of Genvoya, ABT-493 and ABT-530 in a black male subject with baseline low absolute neutrophil count (ANC), leading to premature study drug discontinuation.

Section 3.0 Introduction
Subsection ARV Drug-Drug Interaction Studies with ABT-493 and ABT-530
Last paragraph previously read:

For a more detailed discussion of drug-drug interaction studies please refer to the ABT-493 and ABT-530 Fixed-Dose Combination Investigator's Brochure.[26]

Has been changed to read:

For a more detailed discussion of drug-drug interaction studies please refer to the Investigator's Brochure.[13]

Section 3.0 Introduction
Subsection Clinical Study Results
Last paragraph previously read:

In addition to these studies, 6 Phase 3 studies evaluating approximately 1,940 subjects are currently ongoing. Data from these studies is not yet available.

Has been changed to read:

A total of 2,376 subjects were randomized or enrolled in the registrational studies or supportive Phase 2 studies to receive GLE 300 mg QD and PIB 120 mg QD. Of these, 2,369 subjects received at least 1 dose of study drug.

Section 3.0 Introduction
Subsection Ribavirin (RBV)
Last paragraph, second sentence previously read:

Pregnancy should be avoided (or as directed per the local label) following RBV therapy (Refer to Section 6.1.6).

Has been changed to read:

Pregnancy should be avoided following RBV therapy (Refer to Section 6.1.6).

Section 3.2 Benefits and Risks
Subsection Risks
Fourth paragraph previously read:

Virologic stopping criteria have been incorporated into the study to ensure subjects are exposed to appropriate durations of the regimen.

Has been changed to read:

Virologic failure criteria have been incorporated into the study to ensure subjects are exposed to appropriate durations of the regimen.

Section 4.0 Study Objectives
First bullet previously read:

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

Has been changed to read:

The primary objectives of this study are to assess the efficacy by evaluating the percentage of subjects achieving a 12-week post-treatment sustained virologic response (SVR_{12}) in each treatment arm and safety of ABT-493/ABT-530 plus SOF and RBV in

adults or adolescents with chronic HCV GT1 - 6 infection who previously failed HCV treatment in an AbbVie HCV clinical study, designated as an AbbVie HCV parent study.

Section 5.1 Overall Study Design and Plan: Description
Second paragraph, first sentence previously read:

It is anticipated that approximately 40 HCV infected subjects who have experienced virologic failure following treatment with ABT-493/ABT-530 or 3D or 2D regimens in one of the AbbVie HCV parent studies will be enrolled.

Has been changed to read:

It is anticipated that approximately 50 HCV infected subjects who have experienced virologic failure following treatment with ABT-493/ABT-530 or 3D or 2D regimens in one of the AbbVie HCV parent studies will be enrolled.

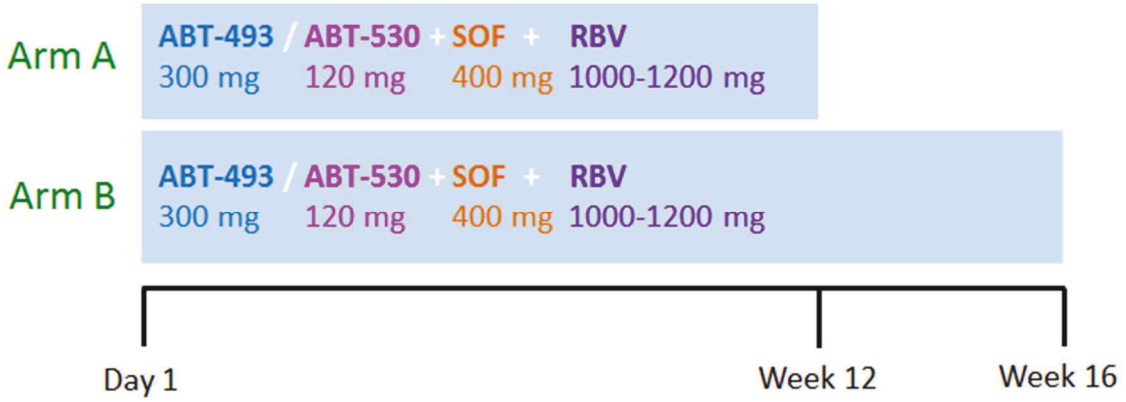
Section 5.1 Overall Study Design and Plan: Description
Fourth paragraph, first sentence previously read:

Arm A will enroll approximately 15 subjects, and Arm B will enroll approximately 25 subjects.

Has been changed to read:

Arm A will enroll approximately 5 subjects, and Arm B will enroll approximately 45 subjects.

Figure 1. Study Schematic (Treatment Period)
Previously read:



Has been changed to read:

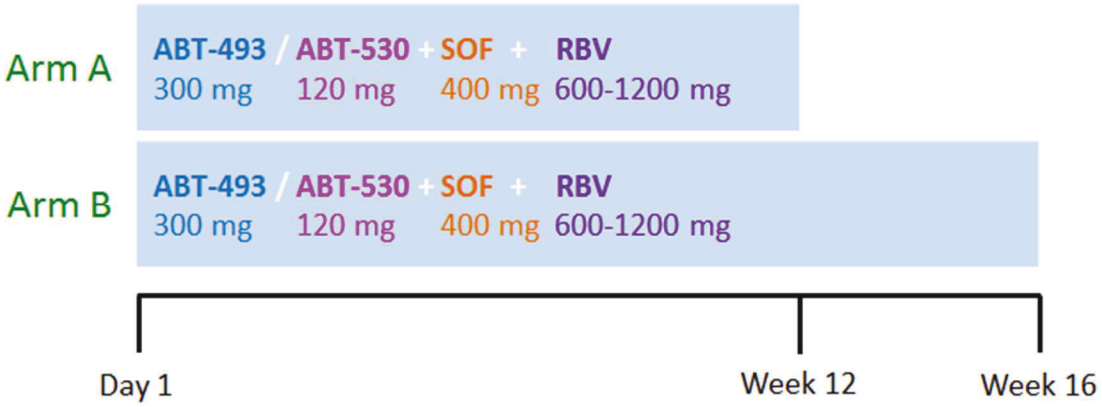


Table 7. Treatment Arm Allocation in Study M15-942
Previously read:

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

* NC = non-cirrhotic; C = cirrhotic.

Has been changed to read:

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

* NC = non-cirrhotic; C = cirrhotic.

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

Section 5.1 Overall Study Design and Plan: Description
First and second bullet previously read:

- Arm A: ABT-493/ABT-530 300 mg/120 mg QD, SOF 400 mg QD and weight-based RBV* BID for 12 weeks.
- Arm B: ABT-493/ABT-530 300 mg/120 mg QD, SOF 400 mg QD and weight-based RBV* BID for 16 weeks.

Has been changed to read:

- Arm A: Subjects will receive orally ABT-493/ABT-530 300 mg/120 mg QD, SOF 400 mg QD, and RBV 600 mg to 1200 mg daily in two divided doses (based on baseline age and weight)* for 12 weeks.
- Arm B: Subjects will receive orally ABT-493/ABT-530 300 mg/120 mg QD, SOF 400 mg QD, and RBV 600 mg to 1200 mg daily in two divided doses (based on baseline age and weight)* for 16 weeks.

Section 5.1 Overall Study Design and Plan: Description
Sixth paragraph previously read:

* RBV will be administered as a weight-based dose (subjects weighing < 75 kg may take RBV orally as 2 tablets in the morning and 3 tablets in the evening which corresponds to a 1000 mg total daily dose; subjects weighing ≥ 75 kg may take RBV orally as 3 tablets in the morning and 3 tablets in the evening which corresponds to a 1200 mg total daily dose), unless required otherwise per local RBV label. Alternative RBV dosing can be used if agreed upon by AbbVie TA MD.

Has been changed to read:

* As defined on Table 8.

Table 8. Ribavirin Dosing Recommendations
Add: new table title and text

Table 8. Ribavirin Dosing Recommendations

Age at Baseline (Years)	Body Weight at Baseline (kg)	Daily Dose (mg)	Number of 200 mg Tablets Per Period of the Day
≥ 18	< 75	1000	2 tablets A.M. + 3 tablets P.M.*
	≥ 75	1200	3 tablets A.M. + 3 tablets P.M.
≥ 12 and < 18	35 – 46	600	1 tablet A.M. + 2 tablets P.M.*
	47 – 59	800	2 tablets A.M. + 2 tablets P.M.
	60 – 74	1000	2 tablets A.M. + 3 tablets P.M.*
	≥75	1200	3 tablets A.M. + 3 tablets P.M.

* The A.M and P.M. pills can be taken in reverse order.

Section 5.1 Overall Study Design and Plan: Description
Last paragraph previously read:

As this is an open-label study, safety will be reviewed by AbbVie. Virologic stopping criteria for subject management, as detailed in Section 5.4.1.1, will be evaluated and applied by the investigator.

Has been changed to read:

As this is an open-label study, safety will be reviewed by AbbVie. Virologic failure criteria for subject management, as detailed in Section 5.4.1.1, will be evaluated and applied by the investigator.

Section 5.1.1 Screening
Last paragraph
Delete: second sentence

In addition, subjects with HCV/HIV-1 co-infection will be provided with an HIV-1 ARV dosing card as described in Section 5.3.1.1.

Section 5.1.1.1 Rescreening
Third paragraph previously read:

Otherwise, subjects may be retested/rescreened only once without approval of the AbbVie TA SD/TA MD, as follows:

Has been changed to read:

Otherwise, subjects may be retested/rescreened only once without approval of the AbbVie Therapeutic Area Scientific Director (TA SD)/TA MD, as follows:

Section 5.1.1.1 Rescreening
First paragraph
Delete: third bullet

HCV genotype indicating co-infection with more than one genotype;

Section 5.1.1.1 Rescreening
Last paragraph previously read:

Subjects being rescreened do not need to be retested for HBV, HIV, HCV genotype and subtype, and FibroScan/liver biopsy.

Has been changed to read:

Subjects being rescreened do not need to be retested for HBsAg, HIV-2 Ab, HCV genotype and subtype, and FibroScan/liver biopsy.

Section 5.1.2 Treatment Period
First paragraph, first sentence previously read:

At the Study Day 1 visit, after all eligibility criteria have been confirmed, subjects will be allocated via IRT into one of two treatment arms based on their HCV genotype, cirrhotic status, and prior treatment experience with PI- and/or NS5Ai-containing regimens before experiencing virologic failure in an AbbVie HCV parent study.

Has been changed to read:

Prior to the Study Day 1 visit, after all eligibility criteria have been confirmed, subjects will be allocated via IRT into one of two treatment arms based on their HCV genotype, cirrhotic status, and prior treatment experience with PI- and/or NS5Ai-containing regimens before experiencing virologic failure in an AbbVie HCV parent study.

Section 5.1.2 Treatment Period
Fifth paragraph previously read:

Virologic stopping criteria will be evaluated and applied by the investigator as detailed in Section 5.4.1.1. Subjects meeting virologic stopping criteria will be discontinued from study drugs.

Has been changed to read:

Virologic failure criteria will be evaluated and applied by the investigator as detailed in Section 5.4.1.1. Subjects meeting on-treatment virologic failure (OTVF) criteria will be discontinued from study drugs.

Section 5.2 Selection of Study Population
Previously read:

The study population consists of chronic HCV GT1 – 6-infected adult subjects who experienced virologic failure while participating in an AbbVie HCV parent study. Subjects must meet all the inclusion criteria and none of the exclusion criteria. In addition, the eligibility of subject to enroll in Study M15-942 will be evaluated at the discretion of AbbVie based upon the characteristics of subject's HCV infection, prior treatment history, and the evolving data from on-going clinical studies.

Has been changed to read:

The study population consists of chronic HCV GT1 – 6-infected adult or adolescent subjects who experienced virologic failure while participating in an AbbVie HCV parent study. Subjects must meet all the inclusion criteria and none of the exclusion criteria. In

addition, the eligibility of a subject to enroll in Study M15-942 will be evaluated at the discretion of AbbVie based upon the characteristics of the subject's HCV infection, prior treatment history, and the evolving data from on-going clinical studies.

Section 5.2.1 Inclusion Criteria
Criterion 1 previously read:

1. Male or female subjects (12 years of age and older, and weighing at least 45 kg), who experienced virologic failure during or after treatment with ABT-493/ABT-530 in an AbbVie HCV parent study. Subjects who have experienced virologic failure during or after receiving ombitasvir/paritaprevir/r + dasabuvir (3D), ombitasvir/paritaprevir/r (2D) in AbbVie HCV parent study may be enrolled at AbbVie's discretion. Treatment in the parent study must have been completed or discontinued at least 1 month prior to the Screening Visit.

Has been changed to read:

1. Male or female subjects must be adults (18 years or more) or adolescents (12 to less than 18 years). Adolescent subjects must weigh at least 35 kg.
2. Subject must have experienced virologic failure during or after treatment with ABT-493/ABT-530 in an AbbVie HCV parent study. Subjects who have experienced virologic failure during or after receiving ombitasvir/paritaprevir/r + dasabuvir (3D), or ombitasvir/paritaprevir/r (2D) in an AbbVie HCV parent study may be enrolled at AbbVie's discretion. Treatment in the parent study must have been completed or discontinued at least 1 month prior to the Screening Visit.

Section 5.2.1 Inclusion Criteria
Criterion 3
Last bullet previously read:

For Women of Childbearing Potential (CBP, as defined in Section), practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1

through at least 4 months after the last dose of study drug or as directed by the local RBV label.

Has been changed to read:

Women of Childbearing Potential (CBP), practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 through at least 4 months after the last dose of study drug or as directed by the local RBV label, whichever is more restrictive.

Section 5.2.1 Inclusion Criteria
Criterion 4 previously read:

If a male subject is sexually active with female partner(s) of CBP, he must agree to practice the protocol specified contraception (Section 5.2.4), from Study Day 1 through 7 months after the last dose of study drug, or as directed by the local RBV label.

Has been changed to read:

If a male subject is sexually active with female partner(s) of CBP, he must agree to practice the protocol specified contraception (Section 5.2.4), from Study Day 1 through 7 months after the last dose of study drug, or as directed by the local RBV label, whichever is more restrictive.

Section 5.2.1 Inclusion Criteria
First paragraph previously read:

In additional to Inclusion Criteria 1 to 8, subjects with HCV/HIV-1 co-infection must also meet the following criteria:

Has been changed to read:

In additional to Inclusion Criteria 1 to 9, subjects with HCV/HIV-1 co-infection must also meet the following criteria:

Section 5.2.1 Inclusion Criteria
Delete: Criterion 9

Subjects who are on stable opioid replacement must be on a therapy with methadone or buprenorphine with or without naloxone for at least 6 months prior to screening.

Section 5.2.1 Inclusion Criteria
Criterion 10, bullet list previously read:

Subjects on a stable ART regimen must have the following:

- CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening; and plasma HIV-1 RNA below < 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV 1 Test, v 2.0) and at least once (HIV-1 < 50 copies/mL) during the 12 months prior to Screening (by an approved plasma HIV-1 RNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTime HIV-1 assay).

Has been changed to read:

- CD4+ count ≥ 200 cells/mm^3 (or CD4+ % ≥ 14%) at Screening;
- and Plasma HIV-1 RNA < 50 copies/mL at Screening (by the COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0) and at least once (HIV-1 < 50 copies/mL) during the 12 months prior to Screening (by an approved plasma HIV-1 RNA quantitative assay including but not limited to: COBAS® Ampliprep/COBAS® Taqman HIV-1 Test, v 2.0 or Abbott RealTi*m*e HIV-1 assay).

Section 5.2.1 Inclusion Criteria
Subsection <u>Rationale for Inclusion Criteria</u>
Previously read:

1, 7 – 10	In order to select the appropriate subject population with appropriate disease characteristics for evaluation

2 – 4	RBV has known teratogenic effects. The impact of ABT-493 and ABT-530 on human pregnancies has not been established. However, assessment of the completed nonclinical reproductive toxicology studies indicates that there is no drug-related effect on teratogenicity/fetotoxicity. In addition, the compounds are non-genotoxic. No adequate human data are available to establish whether or not sofosbuvir poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of sofosbuvir at exposures greater than those in humans at the recommended human dose[16]
5, 6	In accordance with harmonized Good Clinical Practice (GCP)

Has been changed to read:

1, 2, 8 – 11	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
3 – 5	RBV has known teratogenic effects. The impact of ABT-493 and ABT-530 on human pregnancies has not been established. However, assessment of the completed nonclinical reproductive toxicology studies indicates that there is no drug-related effect on teratogenicity/fetotoxicity. In addition, the compounds are non-genotoxic. No adequate human data are available to establish whether or not sofosbuvir poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of sofosbuvir at exposures greater than those in humans at the recommended human dose[16]
6, 7	In accordance with harmonized Good Clinical Practice (GCP)

Section 5.2.2 Exclusion Criteria
Criterion 1 and 2 previously read:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for 4 months after the last dose of study drug, or as directed per the local RBV label.

2. Male subject who is considering fathering a child or whose partner is pregnant during the study or for 7 months after the last dose of the study drug, or as directed per the local RBV label.

Has been changed to read:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for 4 months after the last dose of study drug, or as directed per the local RBV label, whichever is more restrictive.
2. Male subject who is considering fathering a child or whose partner is pregnant during the study or for 7 months after the last dose of the study drug, or as directed per the local RBV label, whichever is more restrictive.

Section 5.2.2 Exclusion Criteria
Criterion 8
Delete: first bullet

Any herbal supplements (including milk thistle) within 2 weeks prior to study drug administration.

Section 5.2.2 Exclusion Criteria
Criterion 10 previously read:

Treatment for an AIDS-associated opportunistic infection (OI) (Appendix D) within 6 months of Screening.

Has been changed to read:

Treatment for an AIDS-Defining Condition (ADC) (Appendix D) within 6 months of Screening.

Section 5.2.2 Exclusion Criteria
Criterion 12, sixth and seventh bullet previously read:

- Platelets < 60,000 cells per mm^3

- Creatinine clearance < 30 mg/dL

Has been changed to read:

- Platelets < 50,000 cells per mm^3 for subjects aged ≥ 18 years, or 40,000 cells per mm^3 for subjects aged < 18 years.
- Calculated creatinine clearance < 30 mL/min

Section 5.2.2 Exclusion Criteria
Criterion 13 and 16 previously read:

13. History of solid organ transplantation, other than liver or kidney transplantation.

16. 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 (see Section 5.6.3 for information about subjects using opioid replacement therapy).

Has been changed to read:

13. History of solid organ transplantation.

16. 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.

Section 5.2.2 Exclusion Criteria
Criterion 19, first sentence previously read:

Current enrollment in another interventional clinical study or previous enrollment in this study.

Has been changed to read:

Current enrollment in another interventional clinical study (except the AbbVie HCV parent study) or previous enrollment in this study.

Section 5.2.2 Exclusion Criteria
Add: new Criterion 20

Subjects who have been confirmed to have documented re-infection. (Refer to Section 5.1).

Section 5.2.2 Exclusion Criteria
Criterion 20 previously read:

Subject has confirmation of HCV reinfection at screening visit (as defined in Section 5.4.1.11).

Has been changed to read:

Subject has confirmation of HCV reinfection at screening visit (as defined in Section 5.4.1.1).

Section 5.2.2 Exclusion Criteria
Subsection Rationale for Exclusion Criteria
Previously read:

1, 2, 8, 10 – 12, 17 – 19	In order to ensure safety of the subjects throughout the study
3, 6, 7, 13 – 19	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
4, 5, 9	To exclude subjects with liver diseases other than HCV

Has been changed to read:

1, 2, 3, 8, 10 – 12, 17 – 19	In order to ensure safety of the subjects throughout the study
6, 7, 13 – 19, 20	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications
4, 9, 11	To exclude subjects with liver diseases other than HCV
5	To exclude subjects with HIV-2 co-infection

Section 5.2.3 Prior and Concomitant Therapy
First paragraph, first and second sentence previously read:

Use of medications (prescription or over-the-counter, including vitamins, herbal supplements, and vaccines) from the time of signing the informed consent through the Treatment Period and 30 days after study drugs are stopped, must be recorded in the electronic case report form (eCRF) at each study visit indicated in the Treatment Period (Appendix C) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. Thereafter, only medications taken for SAEs and treatment of HCV will be recorded in the eCRF at each study visit in the Post-Treatment Period (Appendix C).

Has been changed to read:

Use of medications/supplements (including prescription or over-the-counter, vitamins and/or herbal supplements) or vaccines from the time of signing the informed consent through the Treatment Period and 30 days after study drugs are stopped, must be recorded in the electronic case report form (eCRF) at each study visit indicated in the Treatment Period (Appendix C) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

Section 5.2.3 Prior and Concomitant Therapy
Add: new second paragraph

During the Post-Treatment Period, all medications taken will be recorded until 30 days following the last dose of study drugs. After 30 days post-treatment, during the Post-Treatment Period, only antiviral therapies related to the treatment of HCV and/or HIV and medications prescribed in association with a serious adverse event (SAE) will be recorded in EDC.

Section 5.2.3.2 Prior Prior and Concomitant HIV-1 Therapy
First paragraph previously read:

If a subject is on an HIV-1 ART regimen, it must include at least one of the ARV agents defined on Inclusion Criterion 9 (Section 5.2.1).

Has been changed to read:

If a subject is on an HIV-1 ART regimen, it must include at least one of the ARV agents defined on Inclusion Criterion 10 (Section 5.2.1).

Section 5.2.3.2 Prior Prior and Concomitant HIV-1 Therapy
Last paragraph previously read:

Subjects receiving any other HIV-1 ART in addition to those listed in Inclusion Criterion 9 (Section 5.2.1) would not be eligible for enrollment in the study.

Has been changed to read:

Subjects receiving any other HIV-1 ART in addition to those listed in Inclusion Criterion 10 (Section 5.2.1) would not be eligible for enrollment in the study.

Section 5.2.3.3 Other Concomitant Therapy
First paragraph, first sentence previously read:

Subjects should be on a stable dose of concomitant medications for at least 2 weeks prior to initiation of study drugs.

Has been changed to read:

Subjects should be on a stable dose of concomitant medications for at least 14 days prior to initiation of study drugs.

Section 5.2.3.3 Other Concomitant Therapy
Second paragraph previously read:

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

Has been changed to read:

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, up to 14 days following discontinuation of study drugs, if applicable.

Section 5.2.3.4 Prohibited Therapy
First paragraph previously read:

Subjects must be able to safely discontinue any medications or supplements prohibited to be administered with ABT-493/ABT-530 (listed in Table 9) at least 2 weeks 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. Informed Consent Form must be signed and dated prior to discontinuing any prohibited medications or herbal supplements for the purpose of meeting study inclusion criteria.

Has been changed to read:

Medications or supplements prohibited to be administered with ABT-493/ABT-530 are listed in Table 9. For subjects in the study in countries where ABT-493/ABT-530 (glecapravir/pibrentasvir) has received marketing authorization, any medications in the local label that are contraindicated to be administered with ABT-493/ABT-530 (glecapravir/pibrentasvir) are also considered to be prohibited medications. Subjects must be able to safely discontinue any prohibited medications or supplements at least 14 days 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 14 days following discontinuation of study drugs. The Informed Consent Form must be signed and dated prior to discontinuing any prohibited medications or supplements for the purpose of meeting study inclusion criteria.

Table 8. Medications and Supplements Prohibited with ABT-493/ABT-530 Administration

Previously read:

Medication or Supplement Name
Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine
Tipranavir/r, Atazanavir, Efavirenz, Etravirine, Nevirapine

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

Has been changed to read:

Medication or Supplement Name
Red yeast rice (monacolin K), St. John's Wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin*
Astemizole, cisapride, terfenadine
Tipranavir/r, atazanavir, efavirenz, etravirine, nevirapine
Ethinyl estradiol

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. After signing the informed consent form, subjects receiving these statins should either (a) switch to pravastatin or rosuvastatin at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug or (b) interrupt statin therapy throughout the treatment period beginning at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug and until 14 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to either 1) reduce or limit the pravastatin or rosuvastatin dose in accordance with the ABT-493/ABT-530 (glecapravir/pibrentasvir) product label (if approved in the country) when taking with the study drug; or 2) reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drug, if ABT-493/ABT-530 (glecapravir/pibrentasvir) is not yet approved in the country.

Section 5.2.3.4 Prohibited Therapy
Second and third paragraph previously read:

In addition, refer to the current package insert or product label for SOF and RBV for a complete list of medications prohibited to be used with those drugs, which should not be used at least 2 weeks prior to the first dose of any study drug, throughout the entire Treatment Period and for 30 days following discontinuation of study drugs.

The 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.

Has been changed to read:

In addition, refer to the current package insert or product label for SOF and RBV for a complete list of medications prohibited to be used with those drugs, which should not be used at least 14 days prior to the first dose of any study drug, throughout the entire Treatment Period and for 14 days following discontinuation of study drugs.

Contraceptives and/or hormonal replacement therapies containing only progestins/progestogens (such as those containing norethindrone, desogestrel, or levonorgestrel) or those containing progestins/progestogens with non-ethinyl estradiol estrogens (e.g., esterified or conjugated) may be used with ABT-493/ABT-530 at the discretion of the Investigator.

Section 5.2.3.4 Prohibited Therapy
Fifth paragraph previously read:

For HCV/HIV-1 coinfected subjects, the investigator must refer to the current package insert(s) or product label(s) of a subject's ART regimen for a complete list of medications prohibited to be used with those drugs, which should not be used at least 2 weeks 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.

Has been changed to read:

For HCV/HIV-1 coinfected subjects, the investigator must refer to the current package insert(s) or product label(s) of a subject's ART regimen for a complete list of medications prohibited to be used with those drugs, which should not be used at least 14 days prior to the first dose of any study drug and not use these during the entire Treatment Period and for 14 days following discontinuation of study drugs.

Section 5.2.4 Contraception Recommendations
Subsection Female Subjects
Heading "Females Subjects of CBP must be:"
First bullet previously read:

Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 4 months after the last dose of study drug, or as directed by the local RBV label.

Has been changed to read:

Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 4 months after the last dose of study drug, or as directed by the local RBV label, whichever is more restrictive.

Section 5.2.4 Contraception Recommendations
Subsection Female Subjects
Heading "Females Subjects of CBP must be:"
Second and third sub bullet previously read:

- Bilateral tubal occlusion/ligation
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the CBP trial participant.

Has been changed to read:

- Bilateral tubal occlusion/ligation or bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the CBP trial participant.

Section 5.2.4 Contraception Recommendations
Susection Male Subjects
Previously read:

Subject must be surgically sterile (having performed vasectomy with medical assessment confirming surgical success) or have a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), or, if sexually active with female partner(s) of CBP must agree from Study Day 1 through 7 months (or as directed by the local RBV label), after the last dose of study drug to practice contraception with:

- Condom use.
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable).

Additionally, male subject must agree not to donate sperm from Study Day 1 through 7 months after the last dose of study drug, (or as directed by the local RBV label).

Has been changed to read:

Male subjects who are sexually active with a female partner of CBP, even if the male subject has undergone a successful vasectomy, must agree to use condoms from Study Day 1 through at least 7 months after the last dose of study drug and his female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential). If the local RBV label for the subject has more restrictive recommendations, they must be followed instead.

Male subject must agree not to donate sperm from Study Day 1 through at least 7 months after the last dose of study drug (or as directed by the local RBV label, whichever is more restrictive).

Section 5.3.1.1 Study Procedures
Subsection Pregnancy Testing
First paragraph, first and second sentence previously read:

A serum pregnancy test will be performed for all female subjects of childbearing potential at Screening and Day 1. Additional urine pregnancy tests will be performed every 4 weeks, starting at Day 1 (prior to enrollment) during the treatment period, including at the last Treatment Period visit and until 30 days of last study drug dose, as indicated in Appendix C.

Has been changed to read:

A serum and urine pregnancy test will be performed for all female subjects of childbearing potential at Screening and Day 1. Additional urine pregnancy tests will be performed every 4 weeks, starting at Day 1 (prior to enrollment) during the treatment period, including at the last treatment period visit and until 4 months after the last study drug dose (or as directed by local RBV label, whichever is more restrictive), as indicated in Appendix C.

Table 9. Clinical Laboratory Tests
Column "Other Tests"
Test "Hepatitis A Virus IgM[h]," "Hepatitis A Virus Total[h]," "Hepatitis E Virus IgG[h]" and "Hepatitis E Virus IgM[h]" previously read:

Hepatitis A Virus IgM[h]
Hepatitis A Virus Total[h]
Hepatitis E Virus IgG[h]
Hepatitis E Virus IgM[h]

Has been changed to read:

Anti-Hepatitis A Virus IgM[h]
Anti-Hepatitis A Virus Total[h]
Anti-Hepatitis E Virus IgG[h]
Anti-Hepatitis E Virus IgM[h]

Table 9. Clinical Laboratory Tests
Column "Other Tests"
Add:

HEV RNA[h]

HBV DNA[h]

Table 9. Clinical Laboratory Tests
Column "Other Tests"
Add:

Females not of CBP at Screening do not require pregnancy testing as defined in Section 5.2.1 Criterion 4.

Has been changed to read:

Females not of CBP at Screening do not require pregnancy testing as defined in Section 5.2.1 Criterion 5.

Section 5.3.1.1 Study Procedures
Subsection Liver Diagnostic Testing
Heading "Non-Cirrhotic"
First paragraph previously read:

A liver biopsy within 24 months prior to or during Screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4; or

Has been changed to read:

A liver biopsy within 12 months prior to or during Screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3, Ishak fibrosis score of ≤ 4; or

Section 5.3.1.1 Study Procedures
Subsection Liver Diagnostic Testing
Heading "Cirrhotic"
Second paragraph previously read:

A FibroScan® score of ≥ 12.5 kPa at any time prior to Screening or during Screening period (FibroScan® must be approved by the local regulatory agency); or

Has been changed to read:

A FibroScan® score of ≥ 12.5 kPa at any time prior to Screening or during Screening period (FibroScan® must be approved by the local regulatory agency); or

Section 5.3.1.1 Study Procedures
Subsection Liver Diagnostic Testing
Heading "Cirrhotic"
Fourth and fifth paragraph previously read:

In the absence of a definitive diagnosis of presence or absence of cirrhosis by Fibrotest/APRI using the above criteria (indeterminate FibroTest [0.48 < result < 0.75], or conflicting FibroTest and APRI results [e.g., FibroTest ≤ 0.48, but APRI ≥ 1]), a liver biopsy or FibroScan® is required.

Subjects who are categorized as cirrhotic in this study according to the criteria above must also meet Inclusion Criteria 7 and 8.

Has been changed to read:

In the absence of a definitive diagnosis of presence or absence of cirrhosis by FibroTest/APRI using the above criteria (indeterminate FibroTest [0.48 < result < 0.75], or conflicting FibroTest and APRI results [e.g., FibroTest ≤ 0.48, but APRI ≥ 1]), a liver biopsy or FibroScan® is required.

Subjects who are categorized as cirrhotic in this study according to the criteria above must also meet Inclusion Criteria 8 and 9.

Section 5.3.1.1 Study Procedures
Subsection Child-Pugh (Child-Turcotte-Pugh) Score and Category
First sentence previously read:

The Child-Pugh (Child-Turcotte-Pugh) score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments).

Has been changed to read:

The Child-Pugh (Child-Turcotte-Pugh) score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments) as shown in Table 11.

Section 5.3.1.1 Study Procedures
Subsection Hepatocellular Carcinoma Screening: Liver Ultrasound
Previously read:

Subjects with compensated cirrhosis who do not have a historical qualifying liver ultrasound, CT, or MRI will have an ultrasound performed during Screening. A positive ultrasound result suspicious for HCC at screening will be confirmed with CT scan or MRI during the screening period. Suspicious ultrasound lesions confirmed by CT or MRI at Screening are exclusionary.

Has been changed to read:

HCC screening will be required as a protocol-specified study procedure only at the Screening Study Visit and at the last Post-treatment Study Visit, as indicated in Appendix C, for subjects with compensated cirrhosis only. Between those visits, HCC screening should be performed according to standard of care.

At the Screening Study Visit and at the last Post-treatment Study Visit, subjects with compensated cirrhosis will be required to perform a liver ultrasound to screen for HCC, unless the subject has a historical liver ultrasound, CT or MRI performed for HCC screening within 3 months prior to those visits, in which case the result of the historical US, CT or MRI will be used as the result for that Study Visit assessment. A positive ultrasound result suspicious of HCC will be confirmed with CT scan or MRI. Alternate methods of screening for HCC (i.e., MRI or CT) at a study visit should be discussed with the TA MD.

Section 5.3.1.1 Study Procedures
Subsection HIV-1 ARV Regimen Dosing Card
Delete: subsection title and text

HIV-1 ARV Regimen Dosing Card

For subjects with HCV/HIV-1 coinfection, a dosing card will be provided to subjects on stable ART treatment at each study visit in order to collect information for the last two doses of their HIV-1 ARV medications taken prior to each scheduled pharmacokinetic sample collection as specified in Appendix C.

The information recorded on the dosing cards may be used to guide HIV-1 ARV treatment compliance discussion and to assess pharmacokinetic (PK) collection time relative to HIV-1 ARV dose. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

Site personnel will provide training on its proper use and subjects will be instructed to complete the required information and ensure that entries are up-to-date prior to arrival at

the study site on study visit days. In addition, the investigator or designee will contact the subject approximately 2 days prior to the scheduled pharmacokinetic sample collection date to review the importance of proper HIV-1 ARV administration and documentation of dosing times on the dosing card. The date and time of the phone contact will be entered into source documentation.

Subjects will be required to enter the exact date, time, and number of pills taken for each medication of the ART regimen separately. The information recorded will be reviewed by the site staff; then site staff will enter the information for the last 2 doses taken prior to the scheduled pharmacokinetic sampling into the eCRF. The completed dosing card will be collected by the site personnel on the day of the pharmacokinetic sampling and will be kept as a source record of dosage administration.

In the event that the dosing card is not available at the time of pharmacokinetic sample collection, the site may obtain dosing information via patient interview and record the information for the last 2 doses taken prior to the scheduled pharmacokinetic sampling in the source notes and the eCRF.

Section 5.3.1.1 Study Procedures
Subsection Flow Cytometry, HIV RNA and HIV Resistance Testing Samples
Second paragraph, first sentence previously read:

If a HIV-1 RNA level result of subject on stable HIV-1 ART is ≥ 200 copies/mL, the subject's HIV-1 RNA is to be repeated as noted in Section 5.4.1.2.

Has been changed to read:

If a HIV-1 RNA level result of a subject on stable HIV-1 ART is ≥ 200 copies/mL, the subject's HIV-1 RNA is to be repeated as noted in Section 5.4.1.2.

Section 5.3.2.1 Collection of Samples for Analysis
Previously read:

Blood samples for pharmacokinetic assay of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), RBV, and for the assay of HIV-1 ARVs (if applicable) will be collected by venipuncture at each study visit indicated below and in Appendix C.

All Treatment Period visits except for Study Day 1: two samples (4 mL each) will be collected without regard to the time. 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. The two previous doses of HIV-1 ARVs, if applicable, will be recorded to the nearest minute in the dosing card or the source documents and on the eCRF.

Has been changed to read:

Blood samples for pharmacokinetic assay of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), and RBV will be collected by venipuncture at each study visit indicated below and in Appendix C.

- All Treatment Period visits except for Study Day 1: two samples (4 mL each) will be collected without regard to the time. 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.

Section 5.3.2.2 Handling/Processing of Samples
Previously read:

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, primary metabolite of SOF (GS-331007) RBV and HIV ARVs (if applicable) will be provided by the central laboratory, the Sponsor, or its designee.

Has been changed to read:

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, primary metabolite of SOF (GS-331007) and RBV will be provided by the central laboratory, the Sponsor, or its designee.

Section 5.3.2.3 Disposition of Samples
Previously read:

The frozen plasma samples for the pharmacokinetic assays of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), RBV, HIV ARVs, and archive serum and 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, primary metabolite of SOF (GS-331007), RBV and HIV ARV samples to the reference laboratories following separately provided instructions

Has been changed to read:

The frozen plasma samples for the pharmacokinetic assays of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), RBV, and archive serum and 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, primary metabolite of SOF (GS-331007), and RBV samples to the reference laboratories following separately provided instructions.

Section 5.3.2.4 Measurement Methods
Delete: last paragraph

The samples for HIV ARVs for individual subjects, a group of subjects or for the whole study may be analyzed based on safety, HCV RNA and plasma HIV-1 RNA results. If

requested, the plasma concentrations of HIV ARVs will be determined at PPD using validated assay methods under the supervision of the Drug Analysis Department at AbbVie.

Section 5.3.6 Pharmacokinetic Variable
Delete: second sentence

Values for the pharmacokinetic parameters of ABT-493, ABT-530, SOF, primary metabolite of SOF (GS-331007), and RBV, including apparent clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using population pharmacokinetic modeling procedures.

Section 5.4.1.1 HCV Virologic Criteria
Section title and text previously read:

5.4.1.1 HCV Virologic Stopping Criteria

Virologic stopping criteria are defined as the following:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurement 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 criteria has been confirmed. Subjects meeting the virologic stopping criteria will be discontinued from study drug and will continue to be followed in the Post-Treatment Period, as per Appendix C.

Has been changed to read:

5.4.1.1 HCV Virologic Failure Criteria

The following criteria will be considered evidence of OTVF, for the purposes of subject management, leading to discontinuation of study drug:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurement of > 1 log10 IU/mL above nadir) at any time point during study drug treatment; or
- Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during study drug treatment.

Confirmatory testing should be completed as soon as possible and the subject should remain on study drug treatment until the OTVF criterion has been confirmed. Subjects with confirmed OTVF 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 substitutions until 24 weeks post-treatment (Appendix C).

Post-treatment relapse is defined as confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any post-treatment visit, for subjects who completed treatment (defined as study drug duration ≥ 77 days for subjects who received 12 weeks or ≥ 103 days for subjects who received 16 weeks) and had HCV RNA < LLOQ at the final treatment visit, excluding cases of reinfection, as defined below. HCV reinfection is defined as confirmed HCV RNA ≥ LLOQ after the end of treatment in a subject who had HCV RNA < LLOQ at Final Treatment Visit, along with the post-treatment detection of a different HCV genotype, subtype, or clade compared with baseline, as determined by phylogenetic analysis performed by the sponsor of the HCV NS3, NS5A, and/or NS5B gene sequences. Reinfection in the case of the same HCV subtype is defined as a clade switch, as indicated by the lack of clustering between the baseline and post-treatment sequences by phylogenetic analysis. If phylogenetic analysis is not possible due to technical difficulties, HCV reinfection may be determined with a

confirmed HCV genotype or subtype switch by the Versant HCV Genotype Inno-LiPA Assay v2.0 or Sanger assay.

Section 5.5.1 Treatments Administered
Previously read:

Each dose of study drug (ABT-493/ABT-530, SOF, and RBV) will be dispensed in the form of tablets at the visits listed in Appendix C. The date and time of dosing will be recorded to the nearest minute in the source documents and the eCRF for the 2 days immediately prior to each study visit starting prior to the Week 2 visit. On Study Day 1, subjects will have their dose administered by study site personnel and 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 taken orally as ABT-493/ABT-530 300 mg/120 mg (three × ABT-493 100 mg/ABT-530 40 mg film-coated tablets) QD and with food.

RBV will be provided by AbbVie to the investigator for use in this study. RBV will be provided as 200 mg tablets. RBV has weight-based dosing 1000 to 1200 mg divided twice daily per prescribing information. (For example, subjects weighing < 75 kg may take RBV orally as 2 tablets in the morning and 3 tablets in the evening which corresponds to a 1000 mg total daily dose. Subjects weighing ≥ 75 kg may take RBV orally as 3 tablets in the morning and 3 tablets in the evening which corresponds to a 1200 mg total daily dose.) RBV should be taken with food.

SOF will be provided by AbbVie as 400 mg tablets. SOF will be taken orally as 1 tablet QD, with food.

Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the 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).

Has been changed to read:

Each dose of study drug (ABT-493/ABT-530, SOF, and RBV) will be dispensed in the form of tablets at the visits listed in Appendix C. The date and time of dosing will be recorded to the nearest minute in the source documents (or study drug dosing card) and the eCRF for the 2 days immediately prior to each study visit starting prior to the Week 2 visit.

AbbVie will provide ABT-493/ABT-530 as 100 mg/40 mg film-coated tablets. ABT-493/ABT-530 will be taken orally as three tablets QD (total daily dose of 300 mg/120 mg) and with food.

AbbVie will provide SOF as 400 mg tablets. SOF will be taken orally as 1 tablet QD, with food.

AbbVie will provide RBV as 200 mg tablets. RBV dosing is determined based on the age and weight of the subject at the Day 1 visit, as described in Table 8. RBV should be taken with food. The RBV dose established at Day 1 should be maintained throughout the entire treatment, regardless of ulterior changes in age or weight, unless a dose modification is needed due to toxicity (see Section 6.1.7).

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).

In the event that there is an issue with the study drug supply during the Treatment Period, commercial drug may be provided only with prior AbbVie approval, so that the subject does not experience treatment interruptions. If commercial drug is provided, AbbVie will provide instructions for documentation.

Section 5.5.2.2 Storage and Disposition of Study Drug
Table header row previously read:

Study Drug	Storage Conditions

Has been changed to read:

Study Drug	Storage Conditions*

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

Subjects meeting the eligibility criteria will be enrolled as described in Section 9.3.

Has been changed to read:

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

Section 5.5.4 Selection and Timing of Dose for Each Subject
Second paragraph previously read:

ABT-493/ABT-530 (three tablets) will be dosed QD with food.

Has been changed to read:

ABT-493/ABT-530 (3 tablets) will be dosed QD with food.

Section 5.5.4 Selection and Timing of Dose for Each Subject
Fourth paragraph previously read:

RBV (5 or 6 tablets based on weight) will be dosed BID with food e.g., 2 to 3 tablets taken in the morning, and 3 RBV tablets should be taken in the evening. One of the two daily RBV doses will be taken at the same time as ABT-493/ABT-530 and SOF.

Has been changed to read:

RBV (3 to 6 tablets based on age and weight of the subject at Day 1) will be dosed twice daily with food. For example, if a subject takes 5 tablets of RBV per day, 2 tablets should

be taken in the morning, and 3 tablets should be taken in the evening. One of the two daily RBV doses will be taken at the same time as ABT-493/ABT-530 and SOF. The other RBV dose should be taken approximately 12 hours apart.

Section 5.6.1 Discussion of Study Design and Choice of Control Groups
Second paragraph, last sentence previously read:

The study design will provide additional data on ABT-493/ABT-530 in combination with SOF and RBV, such as response rates in subjects infected with different HCV genotypes, with or without cirrhosis, the PI and/or NS5Ai treatment experience prior to the AbbVie HCV parent study pharmacokinetics, resistance, and the nature of virologic failure (e.g., on-treatment or post-treatment relapse).

Has been changed to read:

The study design will provide additional data on ABT-493/ABT-530 in combination with SOF and RBV, such as response rates in subjects infected with different HCV genotypes, with or without cirrhosis, the PI and/or NS5Ai treatment experience prior to the AbbVie HCV parent study pharmacokinetics, resistance, and the nature of virologic failure (e.g., OTVF or post-treatment relapse).

Section 5.6.3 Suitability of Subject Population
Delete: last paragraph

In order to be enrolled in the study, subjects who are on stable opiate replacement must be on a therapy with methadone or buprenorphine with or without naloxone for at least 6 months prior to screening. This is based on the results from Study M13-602 that evaluated the pharmacokinetic, pharmacodynamic, safety, and tolerability effects of the co-administration of methadone or buprenorphine/naloxone and GLE/PIB in adult subjects on stable opioid therapy, which showed acceptable safety and no relevant pharmacokinetic or pharmacodynamic interactions.

Section 5.6.4.1 Rationale for Dose Selections
First paragraph previously read:

HCV infected patients who were treated and experience virologic failure an AbbVie HCV parent study, will be treated with ABT-493/ABT-530 300 mg/120 mg in combination with SOF 400 mg and weight based RBV for 12 or 16 weeks in the current protocol. The doses of 300 mg ABT-493 and 120 mg ABT-530 were selected based on multiple HCV clinical trials including Studies M14-867, M14-868 and M15-410 in order to optimize efficacy of the combination while maintaining an acceptable safety profile, and to be consistent with the dose selection for ABT-493 and ABT-530 in the currently on-going AbbVie HCV Phase 3 studies.

Has been changed to read:

HCV infected patients who were treated and experienced virologic failure in an AbbVie HCV parent study, will be treated with ABT-493/ABT-530 300 mg/120 mg in combination with SOF 400 mg and weight-based RBV for 12 or 16 weeks in the current protocol. The dose of 300 mg/120 mg of ABT-493/ABT-530 was selected based on multiple HCV clinical trials including Studies M14-867, M14-868 and M15-410 in order to optimize efficacy of the combination while maintaining an acceptable safety profile, is consistent with the dose used in AbbVie HCV Phase 3 studies and is the approved dose for commercial use.

Section 5.6.4.1 Rationale for Dose Selections
Second paragraph, first sentence previously read:

In Studies M14-867, M14-868, high SVR rates have been achieved for the combination of ABT-493 300 mg and ABT-530 120 mg (Table 6).

Has been changed to read:

In Studies M14-867 and M14-868, high SVR rates have been achieved for the combination of ABT-493 300 mg and ABT-530 120 mg (Table 6).

Section 5.6.4.1 Rationale for Dose Selections
Delete: fourth paragraph

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

Section 5.6.4.1 Rationale for Dose Selections
Last paragraph, first and second sentence previously read:

Weight based RBV, 1000 mg to 1200 mg, will be dose-divided to twice daily. This dose is approved for treatment of adult patients with chronic HCV infection in combination with pegIFN.

Has been changed to read:

Weight based RBV, 600 mg to 1200 mg, will be dose-divided to twice daily. This dose is approved for treatment of adult and adolescent patients with chronic HCV infection in combination with pegIFN.

Section 5.6.4.1 Rationale for Dose Selections
Last paragraph, fourth sentence previously read:

In addition, this dose was studied in the absence of pegIFN in Studies M12-267, M12-746, M12-998, M11-652, M11-646, M13-098, M13-389, M13-961, M14-002, and M14-004 and was found to be generally safe and well tolerated and resulted in high SVR rates.

Has been changed to read:

In addition, the RBV dose was studied in the absence of pegIFN in adults in Studies M12-267, M12-746, M12-998, M11-652, M11-646, M13-098, M13-389, M13-961, M14-002, and M14-004, and in adolescents in Study M14-748, and the RBV dose was found to be generally safe and well tolerated and resulted in high SVR rates.

Section 5.6.4.2 Rationale for Duration Selections
First paragraph, fourth sentence previously read:

The interim results from this ongoing study, as summarized in Section 3.0, demonstrate high SVR_{12} rates (mITT rates of 95 – 100%) following a 12-week treatment regimen of ABT-493 and ABT-530 with or without RBV

Has been changed to read:

The interim results from this study, as summarized in Section 3.0, demonstrate high SVR_{12} rates (mITT rates of 95 – 100%) following a 12-week treatment regimen of ABT-493 and ABT-530 with or without RBV

Seciton 5.6.4.2 Rationale for Duration Selections
Second paragraph
Add: new second sentence

Since ABT-493/ABT-530 has pangenotypic activity, subjects with mixed infections and undetermined genotypes will be allowed to be treated in this study.

Seciton 5.6.4.2 Rationale for Duration Selections
Second paragraph, second and third sentence previously read:

The extended treatment duration of 16 weeks for subjects with GT3 infection was based on the study design of the on-going Part 3 of Study M14 868. In Part 3 of Study M14-868, GT3-infected subjects who are treatment-naïve are allocated to the 12 week arm, GT3-infected subjects who are IFN-experienced with compensated cirrhosis are allocated to the 16 week arm, GT3-infected subjects who are IFN-experienced subjects without compensated cirrhosis are allocated at a 1:1 ratio to the 12 week and 16 week treatment arms.

Has been changed to read:

The extended treatment duration of 16 weeks for subjects with GT3 infection was based on the study design of Part 3 of Study M14-868. In Part 3 of Study M14-868, GT3-infected subjects who were treatment-naïve are allocated to the 12 week arm, GT3-

infected subjects who were IFN-experienced with compensated cirrhosis are allocated to the 16 week arm, GT3-infected subjects who were IFN-experienced subjects without compensated cirrhosis are allocated at a 1:1 ratio to the 12 week and 16 week treatment arms.

Seciton 5.6.4.2 Rationale for Duration Selections
Third paragraph, second sentence previously read:

The ABT-493/ABT-530 regimen is being evaluated for 12 week treatment duration in Study M14-172 for subjects with HCV GT1, 2, 4, 5, and 6 infection with compensated cirrhosis, who are either treatment-naïve, or PI- and NS5Ai-naïve.

Has been changed to read:

The ABT-493/ABT-530 regimen was evaluated for 12 week treatment duration in Study M14-172 for subjects with HCV GT1, 2, 4, 5, and 6 infection with compensated cirrhosis, who are either treatment-naïve, or PI- and NS5Ai-naïve.

Seciton 5.6.4.2 Rationale for Duration Selections
Last paragraph, second sentence previously read:

Currently, theThe ABT-493/ABT-530 regimen is beingwas evaluated for a 12 week and 16 week treatment duration in Study M15-410, Part 2 for DAA treatment-experienced subjects with HCV GT1, 4, 5, and 6 infection with or without compensated cirrhosis.

Has been changed to read:

The ABT-493/ABT-530 regimen was evaluated for a 12 week and 16 week treatment duration in Study M15-410, Part 2 for DAA treatment-experienced subjects with HCV GT1, 4, 5, and 6 infection with or without compensated cirrhosis.

Section 6.0 Complaints
Previously read:

For adverse events, please refer to Sections 6.1 through 6.1.7.6.

Has been changed to read:

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 Sections 6.1 through 6.1.7.6. For product complaints, please refer to Section 6.2.

Section 6.1.3 Relationship to Study Drug
In-text table previously read:

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.

Has been changed to read:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

Section 6.1.5 Adverse Event Reporting
First paragraph, last sentence previously read:

Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be faxed to Clinical Pharmacovigilance within 24 hours of the site becoming aware of the serious adverse event.

Has been changed to read:

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 should be faxed to Clinical Pharmacovigilance within 24 hours of the site becoming aware of the serious adverse event.

Section 6.1.5 Adverse Event Reporting
Fifth paragraph previously read:

In case of subject safety concerns or medical emergencies, where the Study TA MD be unavailable, please call the following central back-up number:

Has been changed to read:

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:

Section 6.1.5 Adverse Event Reporting
Last paragraph previously read:

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

Has been changed to read:

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Global and Local Regulations. The reference document used for SUSAR reporting will be the most current version of the Investigator's Brochure. The reference document used

for SUSAR reporting in the EU countries will be the most current version of the Summary of Product Characteristics (SmPC).

Section 6.1.6 Pregnancy
First paragraph previously read:

Subjects and their partners should avoid pregnancy, and males should avoid sperm donation, starting with Study Day 1 until 4 months for females subjects and 7 months for male subjects and their female partners after stopping RBV, or as directed by local RBV label.

Has been changed to read:

Subjects and their partners should avoid pregnancy, and males should avoid sperm donation, starting with Study Day 1 until 4 months for females subjects and 7 months for male subjects and their female partners after stopping RBV, or as directed by local RBV label, whichever is more restrictive.

Table 13. Management of Hemoglobin Decreases
Previously read:

Hemoglobin Reduction in Patients Without Cardiac Disease or History of Cardiac Disease	
Hemoglobin < 10.0 g/dL, but ≥ 8.5 g/dL	Study drugs may be continued
	Reduce RBV dose to 600 mg QD and continue to monitor hemoglobin levels per protocol
	If hemoglobin increases to ≥ 10 g/dL, may increase RBV, with gradual dose increases in 200 mg increments towards original dose
	If Hb decreases to < 8.5 g/dL see appropriate row below
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event
Hemoglobin < 8.5 g/dL	Permanently discontinue RBV and manage the subject as medically appropriate
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event
Reduction in Patients with Stable Cardiac Disease or History of Stable Cardiac Disease	
Hemoglobin decrease of ≥ 2 g/dL during a 4-week treatment period (Hemoglobin ≥ 10 g/dL)	Study drugs may be continued
	Reduce RBV dose to 600 mg QD and continue to monitor hemoglobin levels per protocol
	If a subsequent hemoglobin result is greater than the level that triggered the dose reduction, the investigator may elect to increase RBV, with gradual, 200 mg dose increases towards the original dose
	If the subject has symptoms consistent with their cardiac disease, manage subject as medically appropriate and AbbVie Study TA MD may be contacted
	If hemoglobin does not increase, investigator may manage the subject as medically appropriate. If hemoglobin decreases to < 10 g/dL see appropriate row below
Hemoglobin < 10.0 g/dL, but ≥ 8.5 g/dL	Study drugs may be continued
	Continue at reduced RBV dose as above (or reduce RBV dose to 600 mg QD if this is the initial reduction) and continue to monitor hemoglobin per protocol
	If hemoglobin increases to ≥ 10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose
	If hemoglobin < 10 g/dL despite being for 4 weeks on the reduced RBV dose, permanently discontinue RBV and manage the subject as medically appropriate
Hemoglobin < 8.5 g/dL or < 12 g/dL after 4 weeks of dose reduction	Permanently discontinue RBV and manage the subject as medically appropriate
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event

Has been changed to read:

Hemoglobin Reduction in Patients Without Cardiac Disease or History of Cardiac Disease	
Hemoglobin < 10.0 g/dL, but ≥ 8.5 g/dL	Study drugs may be continued
	Reduce RBV dose to 600 mg QD* and continue to monitor hemoglobin levels per protocol
	If hemoglobin increases to ≥ 10 g/dL, may increase RBV, with gradual dose increases in 200 mg increments towards original dose
	If Hb decreases to < 8.5 g/dL see appropriate row below
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event
Hemoglobin < 8.5 g/dL	Permanently discontinue RBV and manage the subject as medically appropriate
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event
Reduction in Patients with Stable Cardiac Disease or History of Stable Cardiac Disease	
Hemoglobin decrease of ≥ 2 g/dL during a 4-week treatment period (Hemoglobin ≥ 10 g/dL)	Study drugs may be continued
	Reduce RBV dose to 600 mg QD* and continue to monitor hemoglobin levels per protocol
	If a subsequent hemoglobin result is greater than the level that triggered the dose reduction, the investigator may elect to increase RBV, with gradual, 200 mg dose increases towards the original dose
	If the subject has symptoms consistent with their cardiac disease, manage subject as medically appropriate and AbbVie Study TA MD may be contacted
	If hemoglobin does not increase, investigator may manage the subject as medically appropriate. If hemoglobin decreases to < 10 g/dL see appropriate row below
Hemoglobin < 10.0 g/dL, but ≥ 8.5 g/dL	Study drugs may be continued
	Continue at reduced RBV dose as above (or reduce RBV dose to 600 mg QD* if this is the initial reduction) and continue to monitor hemoglobin per protocol
	If hemoglobin increases to ≥ 10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose
	If hemoglobin < 10 g/dL despite being for 4 weeks on the reduced RBV dose, permanently discontinue RBV and manage the subject as medically appropriate
Hemoglobin < 8.5 g/dL or < 12 g/dL after 4 weeks of dose reduction	Permanently discontinue RBV and manage the subject as medically appropriate
	Enter discontinuation into appropriate eCRFs and create corresponding adverse event

* For subjects aged 12 to less than 18, RBV dose reduction should be per local RBV label.

Section 6.1.7.5 Management of Increases in ALT
Previously read:

If a subject experiences a post-baseline ALT value ≥ 5 × ULN that is also ≥ 2 × Baseline a confirmatory test should be performed. If, the ALT is value confirmed ≥ 5 × ULN and ≥ 2 × Baseline the recommendations below should be followed:

- Complete hepatic questionnaire, evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate (e.g., hepatitis A, B and E 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.
- Interrupt study drugs if any of the following is observed at any time:
  - ALT level is ≥ 20 × ULN in the absence of an alternate etiology.
  - Concurrent increases in direct bilirubin or INR or presence/onset of symptoms/signs of hepatitis.
  - At the discretion of the investigator.

Alternate management of confirmed ALT increases requires approval of the AbbVie Study TA MD.

Has been changed to read:

If a subject experiences a post-baseline ALT value ≥ 5 × ULN that is also ≥ 2 × Baseline value, the subject should have a confirmatory test should be performed. If, the ALT is value confirmed ≥ 5 × ULN, and ≥ 2 × Baseline value, the recommendations below should be followed:

- Complete hepatic questionnaire
- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain Anti-HAV IgM, Anti-HAV Total, Anti-HBc IgM, Anti-HBc Total,

Anti-HBs, HBV DNA, HBsAg, Anti-HEV IgM, Anti-HEV IgG and HEV RNA, and other additional tests, as appropriate.

- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs if any of the following is observed at any time:
  - ALT level is ≥ 20 × ULN in the absence of an alternate etiology.
  - Increasing direct bilirubin or INR or onset of symptoms/signs of hepatitis.
  - At the discretion of the investigator.

Alternate management of confirmed ALT increases requires approval of the AbbVie Study TA MD.

Section 6.1.8 Collection of Data Regarding Known AIDS-Associated Opportunistic Infections
Previously read:

6.1.8 Collection of Data Regarding Known AIDS-Associated Opportunistic Infections

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

Has been changed to read:

6.1.8 Collection of Data Regarding Known AIDS-Defining Conditions

HIV-1 infected subjects participating in clinical trials may develop conditions typically associated with AIDS. A list of these known AIDS-Defining Conditions (ADCs) is presented in Appendix D. The events listed in Appendix D will be summarized as HIV-

related events, not as adverse events. These ADCs will be collected from the time of study drug administration until 30 days following discontinuation of study drug.

Section 6.2.2 Reporting
First paragraph, first sentence previously read:

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.

Has been changed to read:

Product Complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint form.

Section 7.0 Protocol Deviations
First paragraph previously read:

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following AbbVie personnel:

Has been changed to read:

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), and the following AbbVie Clinical Monitors:

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

[redacted]
Hub South West Europe & Africa
41-45 Marinou Antypa
Athens, Greece

Office:
Cell:
Fax:
Email: [redacted]

Has been changed to read:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Cell:
Fax:
Email: [redacted]

Section 8.1 Statistical and Analytical Plans
First paragraph
Add: new last sentence

An interim analysis may be conducted for the purpose of regulatory interaction.

Section 8.1 Statistical and Analytical Plans
Third paragraph, last sentence previously read:

Sensitivity analyses of the primary efficacy endpoint, when applicable, will be performed on the intention-to-treat population modified to exclude subjects not of an eligible genotype according to phylogenetic analyses (mITT-GT), and on the mITT-GT population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-GT-VF).

Has been changed to read:

Sensitivity analyses of the primary efficacy endpoint, when applicable, will be performed on the intention-to-treat population modified to exclude subjects who did not achieve SVR_{12} for reasons other than virologic failure (mITT-VF).

Section 8.1.2.1 Primary Efficacy Endpoints
First paragraph, last sentence previously read:

The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval 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.

Has been changed to read:

The number and percentage of subjects achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval using the normal approximation to the binomial distribution, unless the number of virologic failure is less than 5, then the Wilson's score method will be used for the confidence interval instead.

Section 8.1.2.1 Primary Efficacy Endpoints
Last paragraph previously read:

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

Has been changed to read:

A summary of reason for SVR_{12} non-response (e.g., OTVF, relapse, other) will be provided.

Section 8.1.2.2 Secondary Efficacy Endpoints
Second paragraph previously read:

For the analysis of HCV virologic relapse, completion of treatment is defined as any subject with study drug duration of 77 days and 105 days or greater for subjects allocated to treatment durations of 12 weeks and 16 weeks, respectively.

Has been changed to read:

For the analysis of HCV virologic relapse, completion of treatment is defined as any subject with study drug duration of 77 days and 103 days or greater for subjects allocated to treatment durations of 12 weeks and 16 weeks, respectively.

Section 8.1.2.3 Sensitivity Analysis
Last paragraph previously read:

As sensitivity analyses, the number and percentage of subjects in the mITT-GT and mITT-GT-VF populations achieving SVR_{12}, as applicable, will be summarized along with a two-sided 95% confidence interval using Wilson's score interval and the Normal approximation to the binomial distribution by treatment arm and overall.

Has been changed to read:

As sensitivity analyses, the number and percentage of subjects in the mITT-VF populations achieving SVR_{12}, as applicable, will be summarized along with a two-sided 95% confidence interval using Wilson's score interval and the Normal approximation to the binomial distribution by treatment arm and overall.

Section 8.2 Determination of Sample Size
Previously read:

It is anticipated that approximately 40 HCV infected, DAA treatment-experienced subjects who have experienced virologic failure in a AbbVie HCV parent study will be enrolled.

Has been changed to read:

It is anticipated that approximately 50 HCV infected, DAA treatment-experienced subjects who have experienced virologic failure in an AbbVie HCV parent study will be enrolled.

Section 9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Second paragraph, last sentence previously read:

The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Has been changed to read:

The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP and all other applicable regulatory authorities.

Section 9.3 Subject Information and Consent
Second paragraph
Add: new second sentence

The pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed.

Section 10.1 Source Documents
First paragraph
Add: new fourth and fifth sentence

The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

Section 13.0 Completion of Study
Second paragraph, first sentence previously read:

The investigator must retain any records related to the study according to local requirements.

Has been changed to read:

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and other applicable regulatory requirements.

Section 14.0 Investigator's Agreement
Item 1 previously read:

I have received and reviewed the Investigator's Brochure for ABT-493/ABT-530, and the product labeling for SOF and RBV.

Has been changed to read:

I have received and reviewed the Investigator's Brochure for Glecaprevir/Pibrentasvir, and the product labeling for SOF and RBV.

Section 15.0 Reference List
Reference 13 previously read:

AbbVie. ABT-493 Investigator's Brochure Edition 3. 12 September 2014.

Has been changed to read:

AbbVie. Glecaprevir/Pibrentasvir Fixed-Dose Combination Investigator's Brochure Edition 3. 29 August 2017.

Section 15.0 Reference List
Delete: Reference 22, 24, 46 – 50, and 56

22. AbbVie. ABT-530 Investigator's Brochure Edition 3. 12 September 2014.

24. AbbVie. ABT-493/ABT-530 Fixed-Dose Combination Investigator's Brochure Edition 1. 23 September 2015.

46. Lam AM, Espiritu C, Bansal S, et al. Genotype and subtype profiling of PSI-7977 as a nucleotide inhibitor of hepatitis C virus. Antimicrob Agents Chemother. 2012;56(6):3359-68.

47. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370(21):1993-2001.

48. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368(20):1878-87.

49. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370(3):211-21.

50. German P, Mathias A, Pang PS, et al. Lack of a clinically significant pharmacokinetic drug-drug interaction between sofosbuvir (GS-7977) and GS 5885 or GS-9669 in healthy volunteers. 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD). 09-13 November 2012; Boston, MA. Abstract 1888.

56. Johnson VA, Calvez V, Gunthard HF, et al. Update of the drug resistance mutations in HIV-1: March 2013. Top Antivir Med. 2013;21(1):6-14.

Section 15.0 Reference List
Reference 31 previously read:

AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62(3):932-54.

Has been changed to read:

AASLD and IDSA. Patients with HIV/HCV coinfection. Available from: www.HCVGuidance.org. Available on: October 02, 2017.

Appendix B. List of Protocol Signatories
Previously read:

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

Has been changed to read:

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

Appendix C. Study Activities
Subsection Study Activities – Treatment Period
Activity "FibroTest or FibroScan® or Liver Biopsy[f]" previously read:

FibroTest or FibroScan® or Liver Biopsy[f]

Has been changed to read:

FibroTest/APRI or FibroScan® or Liver Biopsy[f]

Appendix C. Study Activities
Subsection Study Activities – Treatment Period
Activity "HgbA1c" previously read:

HgbA1c

Has been changed to read:

Hemoglobin A1c

Appendix C. Study Activities
Subsection Study Activities – Treatment Period
Delete: activity "Dispense/Review HIV-1 ART Dosing Card, if applicable[j]" previously read:

Activity	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 (Arm B Only)	EOT/Premature D/C from Treatment[b]
Dispense/Review HIV-1 ART Dosing Card, if applicable[j]	X (Dispense only)	X	X	X	X	X	X (Review only)

Appendix C. Study Activities
Subsection Study Activities – Treatment Period
Activity "Pharmacokinetic Samples[h]" previously read:

Activity	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 (Arm B Only)	EOT/Premature D/C from Treatment[b]
Pharmacokinetic Samples[h]		X	X	X	X	X	X

Has been changed to read:

Activity	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 (Arm B Only)	EOT/Premature D/C from Treatment[b]
Pharmacokinetic Samples[h]			X	X	X	X	X

Appendix C. Study Activities
Subsection Study Activities – Treatment Period
Table note "a.," "h.," "i.," and "j." previously read:

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

h. PK samples will be collected at each scheduled study visit. Detail regarding timing of samples is provided in Section 5.3.2.1.

i. Child-Pugh Score, Clinical Assessment of Hepatic Decompensation and Liver Ultrasound are only performed for subjects in Arm B (compensated cirrhotic) as described in Section 5.3.1.1.

j. For subjects with HCV/HIV-1 co-infected subjects.

Has been changed to read:

a. All procedures to be performed prior to first dose.

h. PK samples will be collected at each scheduled study visit except Day 1. Detail regarding timing of samples is provided in Section 5.3.2.1.

i. Child-Pugh Score, Clinical Assessment of Hepatic Decompensation and Liver Ultrasound are only performed for subjects with compensated cirrhosis as described in Section 5.3.1.1.

j. For HCV/HIV-1 co-infected subjects.

Appendix C. Study Activities
Subsection Study Activities – Post-Treatment (PT) Period
Activity "Monthly Pregnancy Test (females)[d]" previously read:

Activity	PT Wk 4	PT Wk 12	PT Wk 24 or PT D/C[a]
Monthly Pregnancy Test (females)[d]	X (u)	(PT Weeks 12, 16, 20)	X[c]

Has been changed to read:

Activity	PT Wk 4	PT Wk 12	PT Wk 24 or PT D/C[a]
Monthly Pregnancy Test (females)[d]	X (u)	(PT Weeks 8, 12, 16)	X[c]

Appendix C. Study Activities
Subsection Study Activities – Post-Treatment (PT) Period
Add: new activity "HCC Screening: Liver Ultrasound[h]"

Activity	PT Wk 4	PT Wk 12	PT Wk 24 or PT D/C[a]
HCC Screening: Liver Ultrasound[h]			X

Appendix C. Study Activities
Subsection Study Activities – Post-Treatment (PT) Period
Table note "d." and "e." previously read:

d. Females not of CPB at Screening do not require pregnancy testing. Pregnancy testing should be completed every 4 weeks for 4 months after the last dose of RBV label. At PT Weeks 16 and 20, subjects may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site. Additional testing may be required per local RBV label.
e. Only medications taken for SAEs and for the treatment of HCV will be collected after 30 days post-dosing.

Has been changed to read:

d. Females not of CBP at Screening do not require pregnancy testing. Pregnancy testing should be completed every 4 weeks for 4 months after the last dose of RBV (or as directed per the local RBV label, whichever is more restrictive). At PT Weeks 8 and 16 subjects may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site. Additional testing may be required per local RBV label.
e. Only medications taken for SAEs and for the treatment of HCV and HIV will be collected after 30 days post-dosing.

Appendix C. Study Activities
Subsection Study Activities – Post-Treatment (PT) Period
Table note "g." previously read:

Procedure applicable only to subjects enrolled with cirrhosis.

Has been changed to read:

Required only for subjects with compensated cirrhosis as described in Section 5.3.1.1.

Appendix D. List of AIDS-Associated Opportunistic Infections
Previously read:

Appendix D. List of AIDS-Associated Opportunistic Infections

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

- Aspergillosis
- Bartonellosis

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

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

Cross reference: Guidelines for Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents. Available from: http://aidsinfo nih.gov/guidelines.

Has been changed to read:

Appendix D. List of AIDS-Defining Conditions

Collection of data regarding known AIDS-Defining Conditions (ADCs) is covered in Section 6.1.8.

AIDS-Defining Conditions:

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age > 1 month
- Cytomegalovirus retinitis (with loss of vision)†
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary†

- Mycobacterium tuberculosis of any site, pulmonary,†§ disseminated,† or extrapulmonary†
- Mycobacterium, other species or unidentified species, disseminated† or extrapulmonary†
- Pneumocystis jirovecii pneumonia†
- Pneumonia, recurrent†§
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age > 1 month†
- Wasting syndrome attributed to HIV

* Only among children aged < 13 years.

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged > 13 years.

Cross reference: Morbidity and Mortality Weekly Report (MMWR). AIDS Defining Conditions. 2008. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2 htm.

Appendix E. Clinical Toxicity Grades
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Appendix E. 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

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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

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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

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