1.0 Title Page

Clinical Study Protocol M14-567

A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of the Co-Administration of Ombitasvir/ABT-450/Ritonavir (Ombitasvir/ABT-450/r) With Sofosbuvir (SOF) With or Without Ribavirin (RBV) in Subjects With Genotype 3 Chronic Hepatitis C Virus (HCV) Infection

AbbVie Investigational Product:	Ombitasvir/ABT-450/r
Date:	31 July 2014
Development Phase:	2
Study Design:	This is a randomized, open-label, combination drug study.
EudraCt Number:	2014-003147-35
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc. (AbbVie)*
Sponsor/Emergency Contact:	[redacted]

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.

*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.

1.1 Synopsis

AbbVie Inc.	**Protocol Number**: M14-567
Name of Study Drug: Ombitasvir, ABT-450, ritonavir, sofosbuvir, ribavirin	**Phase of Development:** 2
Name of Active Ingredient: **ombitasvir:** Dimethyl ([(2S,5S)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate **ABT-450:** (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate **ritonavir:** 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)] **sofosbuvir:** (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate **ribavirin:** 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide	**Date of Protocol Synopsis:** 31 July 2014
Protocol Title: A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of the Co-Administration of Ombitasvir/ABT-450/Ritonavir (Ombitasvir/ABT-450/r) With Sofosbuvir (SOF) With or Without Ribavirin (RBV) in Subjects With Genotype 3 Chronic Hepatitis C Virus (HCV) Infection	

Objectives:

The primary objectives of this study are to assess the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response ([SVR_{12}] [HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment]) of co-formulated ombitasvir with ABT-450 and ritonavir (r) (ombitasvir/ABT-450/r) co-administered with sofosbuvir (SOF) with or without ribavirin (RBV) in treatment-naïve and prior (pegIFN, RBV, and/or SOF) treatment-experienced adults with genotype 3 HCV infection without cirrhosis.

The secondary objectives of this study are to assess the percentage of subjects with virologic failure during treatment, the percentage of subjects with post-treatment relapse, and to characterize the pharmacokinetics of direct-acting antiviral agents (DAAs) including ritonavir, SOF, GS-331007 (predominant circulating metabolite of SOF), and RBV (if applicable) in adults with genotype 3 HCV infection.

Investigators: Multicenter, investigator information on file at AbbVie

Study Sites: Approximately 8 sites

Study Population: Adult males and females at least 18 years of age with HCV genotype 3 infection without cirrhosis, who are treatment-naïve or previously treated with pegIFN, RBV, and/or SOF.

Number of Subjects to be Enrolled: Approximately 20 subjects.

Methodology:

This is a Phase 2, randomized, open-label, multicenter study evaluating the safety and efficacy of co-formulated ombitasvir/ABT-450/r co-administered with SOF with or without RBV in treatment naïve and prior (pegIFN, RBV, and/or SOF) treatment-experienced adults with genotype 3 HCV infection without cirrhosis. Approximately 20 subjects will be enrolled across approximately 8 sites globally into one of two arms.

The study consists of:

- **Treatment Period:** Approximately 20 subjects with genotype 3 HCV infection will be randomized 1:1 into the following treatment arms (approximately 10 subjects each):
  - **Arm A:** ombitasvir/ABT-450/r 25 mg/150 mg/100 mg once daily (QD) + SOF 400 mg QD for 12 weeks
  - **Arm B:** ombitasvir/ABT-450/r 25 mg/150 mg/100 mg QD + SOF 400 mg QD + RBV 1000 – 1200 mg divided twice daily (BID) for 12 weeks.

    Randomization to Arms A and B will be stratified by IL28B genotype (CC versus non-CC) and prior treatment status (treatment-naïve versus treatment-experienced). Study drugs should be administered with food. Subject safety laboratory results and virologic failure criteria will be evaluated during the Treatment Period. Upon completion of the Treatment Period or premature discontinuation, subjects will enter the Post-Treatment (PT) Period.
  - **PT Period:** Subjects who complete or prematurely discontinue study drugs in the Treatment Period will be followed for 48 weeks to monitor safety, HCV RNA, the emergence and persistence of resistant viral variants, and assessments of Patient Report Outcomes (PROs).

Methodology (Continued):

Virologic Failure Criteria for Subject Management:

The following criteria will be considered evidence of virologic failure. Subjects demonstrating any of the following will be discontinued from study drug:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment; or
- Failure to achieve HCV RNA < LLOQ by Week 8; or
- Confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA < LLOQ.

Confirmatory testing, where required, should be completed as soon as possible. Also, when confirmation is required, the subject should remain on study treatment until the virologic failure has been confirmed.

If any of the above criteria are met on therapy, the subject will discontinue study treatment as described above.

All subjects who receive at least one dose of study drug in the Treatment Period will be monitored in the Post-Treatment Period for up to 48 weeks following the last dose of study drug.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female at least 18 years of age at time of screening.
2. Chronic HCV infection prior to study enrollment. Chronic HCV infection is defined as one of the following:
   - Positive for anti-HCV Antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
   - HCV RNA > 10,000 IU/mL at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrollment with evidence of chronic hepatitis C disease).
3. Screening laboratory results from the central clinical laboratory indicating HCV genotype 3 infection only.
4. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements and must voluntarily sign and date an informed consent.
5. Absence of cirrhosis, as documented by meeting one of the following criteria (per local standard practice):
   - Liver biopsy within 24 months prior to screening or during screening demonstrating the absence of cirrhosis.
   - Only in the absence of a biopsy within the 24 months prior to screening or during screening:
     - a screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or
     - a screening transient elastography (e.g., FibroScan®) result of < 12.5 kPa.

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

Main Inclusion(Continued):

Subjects with a FibroScan® result that is ≥ 12.5 kPa and < 14.6 kPa, **or** a FibroTest result that is ≤ 0.72 and an APRI ≥ 2, **or** a FibroTest result that is > 0.73 and an APRI ≤ 2, must have a liver biopsy performed within 24 months prior to screening showing no evidence of cirrhosis, or in the absence of an available biopsy results within 24 months prior to screening, may undergo a liver biopsy during screening to rule out cirrhosis.

Main Exclusion:

1. Females who are pregnant or plan to become pregnant or breastfeeding, or males whose partners are pregnant or planning to become pregnant within 7 months (or per local RBV label) after their last dose of study drug.
2. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.
3. Positive test result for Hepatitis B surface antigen (HbsAg) or anti-HIV Ab positive.
4. Current enrollment in another clinical study, previous enrolment in this study, or previous use of any investigational or commercially available anti-HCV therapy (other than interferon, pegIFN, RBV, and or SOF) including previous exposure to telaprevir, boceprevir, ABT-450, or ombitasvir (ABT-267). Subjects who previously participated in trials of investigational anti-HCV agents may be enrolled with approval of the AbbVie Study Designated Physician if they can produce documentation that they received only placebo. Concurrent participation in a non-interventional, epidemiologic, or registry trial may be permitted with approval by the AbbVie Study Designated Physician.
5. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir score > 3 or an Ishak score > 4.
6. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Calculated creatinine clearance (using Cockcroft-Gault method) < 30 mL/min.
   - Albumin < Lower limit of normal (LLN).
   - Prothrombin time/International normalized ratio (INR) > 1.5. Subjects with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the AbbVie Study Designated Physician.
   - Hemoglobin < LLN.
   - Platelets < 120,000 cells per mm^3.
   - Absolute neutrophil count (ANC) < 1500 cells/μL (< 1200 cells/μL for subjects of African descent who are black).
   - Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN.

Investigational Product:	ombitasvir/ABT-450/ritonavir: 12.5 mg/75 mg/50 mg tablet sofosbuvir: 400 mg tablet ribavirin: 200 mg tablet
Dose:	ombitasvir/ABT-450/ritonavir: 25 mg/150 mg/100 mg QD sofosbuvir: 400 mg QD ribavirin weight-based dosing 1000 to 1200 mg BID

Mode of Administration:	Oral
Reference Therapy:	Not applicable
Dose:	Not applicable
Mode of Administration:	Not applicable

Duration of Treatment:

Subject will receive multiple QD doses of ombitasvir/ABT-450/r co-administered with SOF with or without RBV BID for 12 weeks.

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA in IU/mL will be assessed at all Treatment Period visits and at all PT visits.

Criteria for Evaluation (Continued):

Patient Reported Outcomes (PROs):

Health State Utility will be assessed using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L) including its Visual Analog Scale (VAS) component. Fatigue severity will be assessed using the Fatigue Severity Scale (FSS) including its Visual Analog Fatigue Scale (VAFS) component.

Resistance:

The following information will be tabulated and summarized: 1) for all subjects, the variants at baseline at signature resistance-associated amino acid positions relative to the reference sequence, and 2) for subjects who do not achieve SVR_{12}, all post-baseline variants relative to baseline.

Pharmacokinetic:

Intensive pharmacokinetic samples will be collected on Day 1 at 2, 4, and 6 hours post DAA dosing and at the 2-week visit at pre-dose and approximately 2, 4, and 6 hours post DAA dose for measurement of concentrations of ombitasvir, ABT-450, ritonavir, SOF, GS-331007 (predominant circulating metabolite of SOF), and RBV (if applicable). In addition, pharmacokinetic samples will be collected at each study visit during treatment.

Safety:

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

Statistical Methods:

Efficacy:

The primary endpoint is the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The secondary endpoints are the percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment. For the primary and secondary endpoints, the simple percentage of subjects meeting the endpoint will be calculated, and a 2-sided 95% Wilson score confidence interval for a binomial proportion will be computed.

Statistical Methods (Continued):

PROs:

Changes from baseline in the EQ-5D-5L health index score, the visual analogue scale (VAS) response component of the EQ-5D-5L, FSS score, and visual analogue fatigue scale (VAFS) component of the FSS will be summarized for each applicable post-baseline visit by overall and by treatment arm, respectively.

Resistance:

The following resistance information will be provided for all subjects: the amino acid variants at baseline at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence.

The following resistance information will be analyzed for subjects who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA $\geq$ 1000 IU/mL: 1) the amino acid variants in available post-baseline samples identified by population and/or clonal nucleotide sequencing and comparison to the baseline sequence, 2) the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence, and 3) the persistence of resistance-associated amino acid variants by population and/or clonal nucleotide sequencing during the post-treatment period.

Pharmacokinetic:

Individual plasma concentrations of ABT-450, ritonavir, ombitasvir, SOF, GS-331007, and ribavirin will be tabulated and summarized. Individual plasma concentrations of possible metabolites of ABT-450, ombitasvir, and SOF (other than GS-331007) may be tabulated and summarized if measured and sufficient levels of metabolites are observed.

Values for the pharmacokinetic parameters of ombitasvir, ABT-450, ritonavir, SOF, GS-331007, and RBV (if applicable) including the C_{max}, T_{max}, C_{trough}, and AUC will be determined by noncompartmental methods using intensive pharmacokinetic blood sampling data in the study. Additional parameters or summaries may be determined if useful in the interpretation of the data.

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term for each treatment arm and overall. Tabulations by treatment arm will also be provided in which the number of subjects reporting a treatment emergent adverse event (MedDRA preferred term) is presented by severity (mild, moderate, or severe) and relationship to study drugs.

Change from baseline in laboratory tests and vital sign measurements to each time point of collection will be summarized descriptively for each treatment arm. Laboratory test and vital sign values that are potentially clinically significant, according to predefined criteria, will be identified and the number and percentage of subjects with potentially clinically significant values during treatment will be calculated for each treatment arm.

1.2 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APRI	Aspartate aminotransferase-to-Platelet Ratio Index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body Mass Index
BUN	Blood urea nitrogen
CRF	Case report form
CT	Computed Tomography
CYP3A	Cytochrome P450 3A
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EP	European Pharmacopoeia
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Health State Instrument
EU	European Union
FDA	US Food and Drug Administration
FSH	Follicle stimulating hormone
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good laboratory Practice
GS-331007	Predominant circulating metabolite of sofosbuvir
GT	Genotype

HAV-IgM	Hepatitis A virus immunoglobulin M
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
Hemoglobin A1c	Glycated hemoglobin
HEOR	Heath Economics and Outcomes Research
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IL28B	Interleukin 28B
INR	International normalized ratio
IP-10	Interferon gamma-induced protein 10
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
IU	International units
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic acid
MRI	Magnetic Resonance Imaging
NS3A	Nonstructural viral protein 3A
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
OATP1B1	Organic anion transporting polypeptide 1B1
OL	Open-label

Ombitasvir/ABT-450/r	Ombitasvir co-formulated with ABT-450 and ritonavir
PCR	Polymerase Chain Reaction
pegIFN	Pegylated-interferon alfa-2b or alfa-2b
PG	Pharmacogenetic
PK	Pharmacokinetic
POR	Proof of Receipt
PRO	Patient Reported Outcomes
PT	Post-Treatment
QD	Once daily
QTc	QT interval corrected for heart rate
QTcF	QTc using Fridericia's correction formula
r	Ritonavir
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase PCR
SAE	Serious adverse event
sAFP	Serum Alpha-Fetoprotein
SAS	Statistical Analysis System
SD	Standard Deviation
SDP	Study Designated Physician
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
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
TP	Treatment Period
ULN	Upper limit of normal
USP	United States Pharmacopoeia
VAFS	Visual analogue fatigue scale

VAS	Visual analogue scale
WBC	White blood cells

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the plasma concentration-time curve
C_{max}	Maximum observed plasma concentration
C_{trough}	Trough plasma concentration
T_{max}	Time to maximum observed plasma concentration

Definition of Terms

Study Drug	Ombitasvir/ABT-450/r, sofosbuvir, ribavirin
Screening Period	Up to 35 days prior to Study Day 1
Study Day 1	First day of study drug dosing
Treatment Period	Baseline/Day 1 through last dose of study drug
Post-Treatment Period	Day after last dose of study drug through Post-Treatment Week 48 or Post-Treatment Discontinuation

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

Hepatitis C viral (HCV) infection is a global health problem, with 170 million individuals chronically infected worldwide and at risk of developing liver cirrhosis, hepatocellular carcinoma, or both.[1] Cirrhosis develops after prolonged HCV infection.[2] Complications of cirrhosis include hepatic decompensation (ascites, encephalopathy, variceal hemorrhage, hepatorenal syndrome, or hepatic synthetic dysfunction) and hepatocellular carcinoma, which ensues at a rate of about 3% per year.[3-6] Without liver transplantation, decompensated cirrhosis leads to death in 50% to 72% of patients after 5 years.[7] As a result of the high prevalence of HCV infection and resultant complications, HCV is the leading indication for liver transplantation in the United States and the world as a whole.[8]

While the advent of new direct-acting antiviral agents (DAAs) has improved efficacy and reduced the need for interferon in the treatment of HCV, treatment of genotype 3 infection still remains problematic. While genotype 3 accounts for only approximately 7% of infections in the US, it is especially prevalent in India and Pakistan, as well as in many countries in Europe.[9] In many regions of Europe and North America, prevalence of genotype 3 appears to be increasing among younger patients who are active injecting drug users.[10,11] Pegylated interferon and ribavirin for up to 24 weeks is an approved treatment, and is associated with a sustained virologic response (SVR) rate of approximately 66%.[12] Sofosbuvir, a nucleoside nonstructural protein 5B (NS5B) RNA-dependent RNA polymerase inhibitor, is one of the newest DAAs approved by the Food and Drug Administration (FDA), and in clinical studies, sofosbuvir 400 mg daily in combination with ribavirin (RBV) achieved sustained virological response (SVR) rates of 85% in patients with chronic HCV genotype 3 infection when given for 24 weeks, though responses were lower in previously treated patients and those with cirrhosis.[13]

AbbVie currently has a number of DAAs in clinical development for the treatment of HCV infection, two of which have in vitro activity against HCV genotype 3. ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor co-administered with the pharmacokinetic enhancer, ritonavir (ABT-450/r), and

ombitasvir is a NS5A inhibitor. These agents have the potential for co-administration with sofosbuvir in the treatment of genotype 3 HCV infection. An additional AbbVie DAA in development, dasabuvir, is a non-nucleoside NS5B polymerase inhibitor; however, dasabuvir is not active against genotype 3 HCV, and is therefore not included in this trial. Additional information on ABT-450 and ombitasvir is provided below.

ABT-450

ABT-450, (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate, is an NS3/4A protease inhibitor with EC_{50} values in subgenomic replicon stable cell lines of 1.0, 0.21, 5.3, 19 and 0.085 nM against genotypes 1a, 1b, 2a, 3a and 4a, respectively. ABT-450 is metabolized primarily by cytochrome P450 3A4 (CYP3A4) and thus is dosed with ritonavir, a potent CYP3A4 inhibitor, in order to enhance exposures (ABT-450/r). ABT-450/r has been well tolerated in single- and multiple-dose studies in healthy volunteers.

ABT-450/r has a favorable safety, tolerability, and pharmacokinetic profile at doses administered to date and has shown potent antiviral activity at doses of 50/100 mg QD and greater in HCV genotype 1-infected subjects. Additional detailed information about preclinical toxicology, metabolism, pharmacology, and clinical data can be found in the Investigator's Brochure for ABT-450.[14]

Ombitasvir (ABT-267)

Ombitasvir, dimethyl ([(2S,5S)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis {benzene4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]}) biscarbamate hydrate, is an NS5A inhibitor, with EC50 values in subgenomic replicon stable cell lines of 0.014, 0.005, 0.012, 0.004, 0.019 and 0.002 nM against genotypes 1a, 1b, 2a, 2b, 3a, and 4a, respectively.

Ombitasvir has a favorable safety, tolerability, and pharmacokinetic profile at all doses administered to date, and has shown potent antiviral activity at doses of 5 mg QD and greater in HCV genotype 1-infected subjects. Additional detailed information about preclinical toxicology, metabolism, pharmacology and clinical data can be found in the Investigator's Brochure for ombitasvir.[15]

Phase 2 Results with ABT-450 and Ombitasvir in Genotype 3 Infection

The combination of ombitasvir and ABT-450/r has been studied in genotype 1 infection in several Phase 2 trials. However, only one Phase 2a trial (Study M12-998) enrolled subjects infected with genotype 3. In this study, which included subjects with genotypes 1, 2 and 3, 21 genotype 3-infected subjects were enrolled, 11 of whom received ABT-450/r and ombitasvir and 10 of whom received ABT-450/r, ombitasvir, and weight-based RBV 1000 – 1200 mg daily. Antiviral activity was seen in both treatment groups; however, 7 of 10 subjects had suppressed HCV RNA levels (< 25 IU/mL) at the end of 12 weeks of dosing with RBV, compared to 2 of 11 who received treatment for 12 weeks without RBV. SVR was achieved for 5 of 10 subjects who received ombitasvir + ABT-450/r + RBV, compared to 1 of 11 who received ombitasvir + ABT-450/r alone.

Integrated Safety Results

The interferon (IFN)-free regimen of ABT-450/r, ombitasvir, and the non-nucleoside NS5B polymerase inhibitor, dasabuvir, has been studied with and without RBV in over 2,300 genotype 1-infected patients in Phase 3 trials across a variety of patient populations, including patients with compensated cirrhosis. Based on these data, this 3-DAA regimen with or without RBV is safe and well tolerated in treatment-naïve and treatment-experienced HCV genotype 1-infected subjects including those with compensated cirrhosis. In a Phase 2 trial, Study M12-998, 61 subjects were treated with ombitasvir/ABT-450/r with or without RBV for 12 weeks. Based on findings from this study, the safety profile of ombitasvir/ABT-450/ritonavir with or without RBV appears comparable to that of ombitasvir/ABT-450/ritonavir plus dasabuvir with or without RBV, respectively.

A summary of treatment-emergent adverse events from pooled analyses of data from the Phase 3 studies in genotype 1-infected subjects is presented in Table 1. A majority of subjects experienced at least one event, but most subjects experienced events that were mild in severity. Rates of severe adverse events and adverse events leading to discontinuation were low across studies, but numerically higher in the study of subjects with cirrhosis.

Table 1. Overview of Treatment-Emergent Adverse Events (AE)

	Placebo-Controlled		Regimen-Controlled		Cirrhotics	
	12-wk 3-DAA + RBV	12-wk PBO	12-wk 3-DAA + RBV	12-wk 3-DAA	12-wk 3-DAA + RBV	24-wk 3-DAA + RBV
Events, %	N = 770	N = 255	N = 401	N = 509	N = 208	N = 172
Subjects ≥ 1 AE	89.0	76.9	82.8	75.0	91.8	90.7
Severe AE	3.5	0.4	1.0	1.2	6.7	7.6
Grade 3 or 4 AE	3.9	0.8	3.0	2.0	7.7	8.1
Serious AE	2.1	0.4	2.2	1.4	6.3	4.7
AE leading to discontinuation	0.8	0.4	0.5	0.4	1.9	2.3
Deaths	0.1[a]	0	0	0	0	0

wk = week, PBO = placebo

a. Lung cancer.

The most common adverse events regardless of causality are listed in Table 2. Adverse events that occurred with an incidence at least 5% greater in the 3-DAA + RBV regimen compared to placebo were considered to be adverse drug reactions related to the study treatment. These include fatigue, nausea, pruritus, insomnia, asthenia, and anemia. The frequency of these events was generally lower in the arm treated without RBV. In general, rates of adverse events were similar in patients with cirrhosis versus patients without cirrhosis.

Table 2. Treatment-Emergent Adverse Events with ≥ 10% Frequency in at Least One Arm of the Analysis and Rates of Key Post-Baseline Lab Abnormalities

	Placebo-Controlled		Regimen-Controlled		Cirrhotics	
Treatment-Emergent Adverse Events, %	**12-wk 3-DAA + RBV**	**12-wk PBO**	**12-wk 3-DAA + RBV**	**12-wk 3-DAA**	**12-wk 3-DAA + RBV**	**24-wk 3-DAA + RBV**
	N = 770	**N = 255**	**N = 401**	**N = 509**	**N = 208**	**N = 172**
Headache	34.3	29.8	24.4	25.1	27.9	30.8
Fatigue	34.2	26.3	29.9	26.5	32.7	46.5
Nausea	22.3	14.9	15.7	8.4	17.8	20.3
Pruritus	15.7	4.3	12.0	6.1	18.3	19.2
Insomnia	14.0	7.5	12.2	5.1	15.4	18.0
Diarrhea	13.5	9.0	8.7	11.4	14.4	16.9
Asthenia	13.5	6.7	9.0	3.9	13.9	12.8
Rash	10.0	5.9	6.2	3.7	11.1	14.5
Cough	8.7	5.1	6.7	4.7	11.5	11.0
Irritability	5.3	4.7	3.2	3.1	7.2	12.2
Anemia	5.3	0	7.5	0.2	7.7	10.5
Dyspnea	9.7	5.5	4.7	2.2	5.8	12.2
Laboratory Events, %	**N = 765**	**N = 254**	**N = 401**	**N = 509**	**N = 208**	**N = 172**
Hemoglobin						
< 10 g/dL (Gr 2)	5.5	0	6.2	0	7.2	11.0
< 8.0 g/dL (Gr 3)	0.1	0	0.5	0	1.4	0.6
ALT						
> 5 × ULN (Gr 3)	1.2	3.9	0.7	0.2	2.9	0
Bilirubin						
> 3 × ULN (Gr 3)	2.6	0	5.7	0.4	13.5	5.2

wk = week, PBO = placebo

Note: Percentages of laboratory events are based on the number of subjects with at least one post-baseline value.

Transient elevations in total (predominantly indirect) bilirubin have been observed, due to ABT-450 inhibition of the bilirubin transporters OATP1B1 and OATP1B3 and RBV-induced hemolysis. The elevations generally peaked by Weeks 1 and 2, declined through the end of treatment and returned to within the normal range by 4 weeks

post-treatment. Hyperbilirubinemia occurred less frequently in subjects treated with 3 DAAs without RBV compared to 3 DAAs with RBV. The frequency and degree of hyperbilirubinemia were higher in subjects with cirrhosis, but the temporal pattern of elevation followed by resolution was similar and few episodes were symptomatic. Grade 2 + hemoglobin reductions occurred in 6% of subjects without cirrhosis who received the 3-DAA + RBV regimen for 12 weeks, and 7% and 11% of subjects with cirrhosis who received the 3-DAA + RBV regimen for 12 and 24 weeks, respectively. Grade 3 hemoglobin values were rare. The decline in hemoglobin was largely managed with RBV dose reductions. Anemia observed during the clinical trials was largely attributable to the presence of RBV as it was not observed when the 3-DAA regimen was administered without RBV.

Transient asymptomatic post-baseline serum ALT elevations of > 5 × ULN occurred at a frequency of 1% across active treatment arms and were evaluated by an external panel of expert hepatologists. The ALT elevations were asymptomatic, usually occurred within the first 4 weeks of treatment and typically declined with ongoing treatment. A disproportionate number of the cases were in women on concurrent systemic estrogen-containing therapy (i.e., contraceptives or hormone replacement) and discontinuation of the hormonal therapy with continuation or brief interruption of the DAA regimen led to resolution in serum ALT elevation. Concomitant use of systemic estrogen-containing medications is a risk factor for these post-baseline elevations in serum ALT. No ALT elevations > 5 × ULN were observed in subjects receiving progestins only or in subject receiving topical vaginal estrogen preparations. Among the cases of serum ALT elevation thought to be related to the DAA regimen, none resulted in hepatic dysfunction and they generally resolved or improved with ongoing treatment. All cases had resolved completely in the post-treatment follow-up.

ABT-450/ritonavir and ombitasvir (and its major inactive human metabolites) had no effects on embryo-fetal development in rodent and/or nonrodent species at maximal feasible exposures that provided AUC multiples at least 4-fold higher than exposure at the

recommended clinical doses. Clinical studies in women who are pregnant have not been conducted.

Sofosbuvir

Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor 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.[16] Sofosbuvir has demonstrated potent activity when administered to HCV genotype 3-infected subjects in combination with RBV.

After oral administration, sofosbuvir is rapidly converted to the predominant circulating metabolite GS-331007 that accounts for greater than 90% of drug related material system exposure, while sofosbuvir accounts for approximately 4% of drug related material. Sofosbuvir peak plasma concentrations occurred 0.5 to 2 hours post-dose and GS-331007 peak plasma concentrations were reached 2 to 4 hours post dose.[16]

Sofosbuvir is a substrate of drug transporters P-gp and breast cancer resistance protein (BCRP), while GS-331007 is not. Co-administration of sofosbuvir with drugs that are P-gp inducers in the intestines may decrease sofosbuvir plasma concentrations leading to reduced effect and are not recommended for co-administration with sofosbuvir. Drugs that inhibit P-gp and BCRP may increase sofosbuvir plasma concentrations without increasing GS-331007 plasma concentrations; thus, no precautions in co-administration are warranted. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP.[16]

Sofosbuvir is a prodrug extensively metabolized in the liver to the pharmacologically active nucleoside analog triphosphate, GS-461203. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro.[16]

The majority of the sofosbuvir dose recovered in urine was GS-331007 while 3.5% was recovered as sofosbuvir, suggesting that renal clearance is the major elimination pathway

for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively.[16]

Sofosbuvir was well tolerated in clinical trials, with ≤ 1.5% of subjects discontinuing therapy with SOF + RBV or SOF + pegIFN + RBV for 12 weeks. The most frequently reported adverse events were typically mild to moderate and included fatigue, nausea, and headache.

Sofosbuvir has in vitro activity against genotype 3a in the replicon system.[19] Sofosbuvir in combination with RBV resulted in SVR rates of 56% and 92% – 94% in treatment-naïve genotype 3-infected subjects when given for 12 and 24 weeks, respectively.[13,17] Response rates were lower in treatment-experienced subjects, especially those with cirrhosis, who had an SVR rate of 60% with 24 weeks of treatment.[13] Sofosbuvir was also studied in a smaller trial in combination with the NS5A inhibitor daclatasvir. No clinically relevant interactions were observed, and significant antiviral activity was observed, with 89% of 18 treatment-naïve subjects with genotype 3 infection achieving SVR with 24 weeks of treatment.[23] No clinically meaningful drug interactions have been observed when sofosbuvir was combined with NS5A inhibitors (daclatasvir,[19] ledipasvir[21]) or the protease inhibitor simeprevir.

An ongoing Phase 1 trial, Study M14-527, is assessing the safety and pharmacokinetics of the combination of ombitasvir/ABT-450/r with or without dasabuvir plus sofosbuvir (SOF) in healthy volunteers for up to 14 days. No significant pharmacokinetic interactions are expected, and no safety signals of concern have been reported from that trial. The current study is intended to examine the safety and antiviral activity of ombitasvir/ABT-450/r in combination with SOF with or without RBV in treatment-naïve and treatment-experienced subjects with chronic genotype 3 HCV infection.

3.1 Differences Statement

A previous trial evaluated ABT-450/r and ombitasvir with or without RBV in genotype 3 infection (Study M12-998), and the combination of ombitasvir/ABT-450/r

with SOF is being assessed in healthy volunteers in an ongoing drug interaction study (Study M14-527). In addition, Phase 3 studies have evaluated SOF plus RBV for genotype 3 infection. This is the first study to evaluate the combination of the co-formulated ombitasvir/ABT-450/r tablet co-administered with SOF with or without RBV in HCV genotype 3-infected subjects.

3.2 Benefits and Risks

Based on results of the Phase 2 Study M12-998 and the known activity of SOF, it is expected that the combination of ombitasvir/ABT-450/r and SOF with or without RBV may lead to SVR for a significant proportion of subjects. However, the likelihood of achieving SVR in this study is unknown. Risks of the study regimen include drug toxicity and virologic failure, which may result in selection of drug resistance.

Risk of Toxicity

Combination dosing of ABT-450/r with ombitasvir, with or without dasabuvir, has generally been well tolerated in healthy volunteers and HCV-infected subjects. Both groups have been dosed with and without RBV, for lengths up to 24 weeks in HCV genotype 1-infected subjects in Phase 3 studies. Preclinical toxicology studies have assessed the toxicity of ombitasvir for up to 6 months, and ABT-450 for up to 9 months. No dose-limiting toxicities have thus far been observed in animal studies, or in humans receiving the doses of ABT-450/r and/or ombitasvir used in this study. SOF has likewise been well tolerated in clinical trials when given for up to 24 weeks with or without RBV. Preclinical toxicology studies showed heart inflammation and degeneration in rats at (GS-331007) exposures approximately 29-fold higher than those seen in humans at the recommended clinical dose. These findings were not observed in dogs or mice at similar or higher exposures, when treated for 9 and 3 months, respectively. ABT-450/r and ombitasvir have not previously been dosed together in combination with SOF in HCV-infected subjects, so there is a risk of toxicity associated with the combination, but given the benign safety profile of both ombitasvir/ABT-450/r and SOF, the likelihood is low. A drug interaction study in healthy volunteers, Study M14-527, is ongoing. No

safety findings of concern have been reported in healthy volunteers receiving ombitasvir/ABT-450/r, dasabuvir and SOF for up to 14 days. Study drug dosing in the current study will not begin until preliminary pharmacokinetic results from Study M14-527 confirm absence of clinically meaningful drug-drug-interactions. Study drug dosing in the current study will not begin until preliminary pharmacokinetic results from Study M14-527 confirm absence of clinically meaningful drug-drug interactions.

Risk of Treatment Failure

The likelihood of successfully curing genotype 3-infected subjects with a regimen containing ombitasvir/ABT-450/r and SOF is unknown. However, ABT-450/r plus ombitasvir showed modest efficacy against genotype 3 when administered for 12 weeks in a previous study (Study M12-998), which was improved with the addition of RBV,[18] and the combination of SOF plus RBV is also active against genotype 3.[13] Furthermore, in a small trial, the combination of SOF and the NS5A inhibitor daclatasvir achieved SVR in 89% of 18 treatment-naïve subjects with genotype 3 HCV infection.[23] Hence, it is reasonable to predict that the combination (with or without RBV) will be efficacious in a significant proportion of subjects in this study.

It is not known what impact prior treatment experience will have on the risk of treatment failure in this study.

In summary, the risks associated with the individual study drugs to be administered in Study M14-567 have been well characterized and appear limited and manageable. Subjects will be closely monitored for any potential risks which may occur when the DAAs are dosed in combination, including risks of toxicity and of virologic failure. Given the potential benefit of achieving cure in a population of HCV-infected subjects with limited available treatment options, as well as the manageable risks associated with the planned therapy, the risk-benefit comparison is considered favorable.

4.0 Study Objective

4.1 Primary Objectives

The primary objectives of this study are to assess the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response ([SVR_{12}] [HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment]) of co-formulated ombitasvir with ABT-450 and ritonavir (ombitasvir/ABT-450/r) co-administered with SOF with or without RBV in treatment-naïve and prior (pegIFN, RBV, and/or SOF) treatment-experienced adults with genotype 3 HCV infection without cirrhosis.

4.2 Secondary Objectives

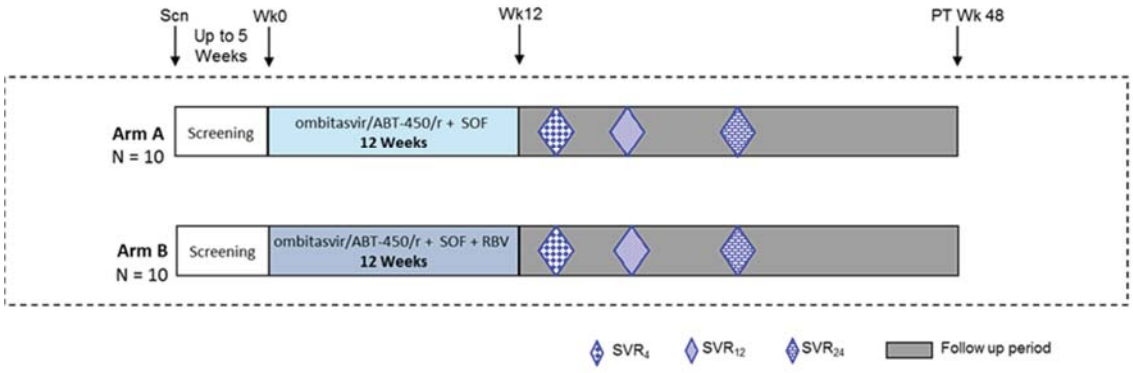
The secondary objectives of this study are to assess the percentage of subjects with virologic failure during treatment, to assess the percentage of subjects with post-treatment relapse, and to characterize the pharmacokinetics of DAAs including ritonavir, sofosbuvir, GS-331007 (predominant circulating metabolite of SOF), and RBV (if applicable) in adults with genotype 3 HCV infection.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 2, randomized, open-label, multicenter study evaluating the safety and efficacy of co-formulated ombitasvir/ABT-450/r co-administered with SOF with or without RBV in treatment-naïve and prior (pegIFN, RBV, and/or SOF) treatment-experienced adults with genotype 3 HCV infection without cirrhosis. Approximately 20 subjects will be enrolled across approximately 8 sites globally into one of two treatment arms (Figure 1).

Figure 1. Study Design



These subjects will be randomized to Arms A and B in a 1:1 ratio (approximately 10 subjects each). Randomization to Arms A and B will be stratified by IL28B genotype (CC versus non-CC) and prior treatment status (treatment-naïve versus treatment-experienced).

- **Arm A:** ombitasvir/ABT-450/r 25 mg/150 mg/100 mg and SOF 400 mg QD for 12 weeks
- **Arm B:** ombitasvir/ABT-450/r 25 mg/150 mg/100 mg and SOF 400 mg QD with RBV 1000 – 1200 mg BID for 12 weeks

RBV dosing will be weight-based, either 1000 mg or 1200 mg daily divided BID per local label (e.g., < 75 kg = 1000 mg daily divided BID or ≥ 75 kg = 1200 mg daily divided BID).

The duration of the study will be up to 60 weeks long (not including a screening period of up to 35 days) consisting of two periods: the Treatment Period and the Post-Treatment (PT) Period. All subjects who complete or prematurely discontinue the Treatment Period will be followed for 48 weeks to monitor safety, HCV RNA, the persistence of resistant viral mutants, and assessment of Patient Reported Outcomes (PROs).

Subjects will be either HCV treatment-naïve or previously treated with interferon, pegIFN, RBV, and/or SOF. Categorization of prior HCV treatment experience will be based on the last prior HCV treatment course. This prior HCV therapy must have been completed no less than 2 months prior to the Screening Visit.

Subjects whose only prior treatment experience included standard (non-pegylated) interferon will not be eligible. However, subjects with a prior history of non-pegylated interferon therapy who were subsequently treated with pegIFN/RBV, pegIFN/RBV plus SOF, or SOF plus RBV may be enrolled.

Subjects with previous HCV RNA measurements that provide complete documentation of the type of response to prior treatment with pegIFN/RBV without sofosbuvir, pegIFN/RBV plus sofosbuvir, or sofosbuvir plus RBV therapy will be categorized as one of the following:

- Prior pegIFN/RBV null-responder: failed to achieve a 1 $\log_{10}$ IU/mL reduction in HCV RNA by Week 4 or a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior pegIFN/RBV treatment course;
- Prior pegIFN/RBV partial responder: achieved at least a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior pegIFN/RBV treatment course, but failed to achieve HCV RNA undetectable at the end of treatment;
- Prior SOF breakthrough/non-responder: HCV RNA quantifiable at the end of treatment with SOF plus pegIFN/RBV, or SOF plus RBV;
- Prior HCV therapy relapser: achieved HCV RNA unquantifiable (detected or undetected) at end of a prior treatment course of pegIFN/RBV, SOF plus pegIFN/RBV, or SOF plus RBV, but HCV RNA was quantifiable following cessation of therapy.

Subjects treated with pegIFN/RBV without SOF, pegIFN/RBV plus SOF, or SOF plus RBV therapy with a less well-characterized treatment experience, including those subjects with incomplete HCV RNA and treatment date documentation, will require approval by

the AbbVie Study Designated Physician for the determination of study eligibility. These subjects will be categorized as one of the following:

- Prior HCV therapy relapse/breakthrough: Achieved at least one documented result of HCV RNA unquantifiable (detected or undetected) during a prior treatment course of pegIFN/RBV, SOF plus pegIFN/RBV, or SOF plus RBV;
- Prior HCV therapy non-responder: No documented result of HCV RNA unquantifiable (detected or undetected) during a previous treatment with pegIFN/RBV, SOF plus pegIFN/RBV, or SOF plus RBV treatment with insufficient data available to distinguish between breakthrough, partial, and null responder;
- pegIFN intolerant (Category does not apply to subjects previously treated with SOF plus RBV): Did not meet any definitions of treatment-failure and discontinued pegIFN-containing therapy prior to a full course of treatment due to pegIFN intolerability.
- pegIFN experienced – other (Category does not apply to subjects previously treated with SOF plus RBV): Includes pegIFN/RBV or SOF plus pegIFN/RBV experienced subjects who do not have adequate documentation of response to be included in any of the above categories.

5.1.1 Screening

At the Screening Visit, subjects who provided written (signed and dated) informed consent prior to any study specific procedures, will receive a unique subject number via an Interactive Response Technology (IRT) system and will undergo the study procedures indicated within the Study Activities table and detailed in Section 5.3.1.1 associated with the Screening Visit. The investigator will evaluate whether the subject meets eligibility criteria, as specified in Section 5.2.1 and Section 5.2.2. The informed consent process and all screening procedures performed will be recorded and documented. Eligible subjects have up to 35 days following the Screening Visit to enroll into the study. Subjects who require a liver biopsy to determine eligibility should meet all of the other inclusion and none of the exclusion criteria before undergoing a liver biopsy.

The study was designed to enroll approximately 20 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

5.1.1.1 Rescreening

Subjects who meet all eligibility criteria with the exception of up to three exclusionary laboratory parameters may rescreen once within the 35-day screening period without prior AbbVie approval. However, subjects with any of the following exclusionary values will not be allowed to rescreen: exclusionary HCV genotype, a positive hepatitis B surface antigen (HBsAg), positive human immunodeficiency virus (HIV) antibody, or confirmed pregnancy. Subjects with more than three exclusionary laboratory results will require approval from the AbbVie Study Designated Physician prior to rescreening. Subjects being rescreened because of exclusionary laboratory parameter(s) must have the related panel(s) repeated (e.g., exclusionary hemoglobin requires a repeat hematology panel) within the same screening period.

For subjects who do not meet the study eligibility criteria, the site personnel must register the subject as a screen failure in both IRT and electronic data capture (EDC) systems.

5.1.2 Treatment Period

Non-cirrhotic subjects with HCV genotype 3 infection who meet the eligibility criteria will be randomized via IRT in a 1:1 ratio to either ombitasvir/ABT-450/r co-administered with SOF (Arm A) or ombitasvir/ABT-450/r co-administered with SOF and RBV (Arm B). The Treatment Period of the study consists of 12 weeks of open-label treatment.

All DAAs will be administered once daily (QD) as detailed below.

- ombitasvir/ABT-450/r 25 mg/150 mg/100 mg QD
- SOF 400 mg QD

RBV dosing, if applicable, will be weight based, either 1000 mg or 1200 mg daily divided BID per local label (e.g., < 75 kg = 1000 mg daily divided BID or ≥ 75 kg = 1200 mg daily divided BID).

Subjects will receive instructions regarding study drug administration and dosing and will be administered the first doses of study drugs at the site on Study Day 1. All subjects will continue to return to the site on an outpatient basis through the end of their Treatment Period for study procedures as identified in Table 4; site personnel should make every reasonable effort to ensure visit schedule adherence. It should be noted and reinforced to subjects that SOF is supplied with the exact amount of tablets needed between the study drug dispensation visits in Table 4. Subjects who cannot complete study visits according to schedule will need assistance in managing their study drug supply between visits to ensure they do not run out of study drugs prior to their next study visit.

Safety and efficacy evaluations will occur through the study. As this is an open-label study, the safety data will be reviewed by AbbVie during the Treatment Period of the study. Virologic failure criteria for subject management, as detailed in Section 5.4.1.1, will be evaluated and applied by the investigator.

Plasma samples for pharmacokinetic analysis will be collected as detailed in Section 5.3.2.1.

Safety and tolerability of the treatments will be assessed throughout the study. Laboratory testing will include chemistry, hematology, and urinalysis (Table 6). Ongoing review of the data is planned in order to determine if subjects meet the virologic failure criteria (Section 5.4.1.1). Virologic failure criteria will be evaluated and applied by the Investigator as detailed in Section 5.4.1.1.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as defined in Table 4 and as described in Section 5.4.1. Ideally, this should occur on the day of the study drug discontinuation, but is recommended to be no later than 2 days after their final dose of

study drugs and prior to initiation of any other anti-HCV therapy. Subjects who complete or prematurely discontinue study drug will immediately start the PT Period and be monitored for safety, virologic failure, and resistance as detailed in Section 5.4.1.1.

5.1.3 Post-Treatment (PT) Period

All subjects who receive at least one dose of study drugs will be monitored for safety, HCV RNA, the emergence and/or persistence of resistance viral variants, and assessment of PROs for an additional 48 weeks following the last dose of study drugs. Subjects will return to the study site as outlined in Table 5 for PT procedures. The PT Period will begin the day after the last dose of study drugs. Subjects who prematurely discontinue the PT Period should return to the site for a PT Discontinuation Visit as outlined in Table 5.

5.2 Selection of Study Population

The subject population consists of HCV genotype 3-infected treatment-naïve and prior (pegIFN, RBV, and/or SOF) treatment-experienced adult subjects without cirrhosis. Subjects who meet all the following inclusion criteria and who do not meet any of the following exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Male or female at least 18 years of age at time of screening.
2. Female who is:
    - practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle); or
    - sexually active with female partners only; or
    - not of childbearing potential, as defined as:
        - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate and confirmed by a follicle-stimulating hormone (FSH) level indicating a postmenopausal state); or

- surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s); or

- of childbearing potential and sexually active with male partner(s):
  - currently using at least one effective method of birth control at the time of screening and agrees to practice two effective methods of birth control while receiving study drugs (as outlined in the subject information and consent form or other subject information documents),

    For subjects whose study drug regimen will not include RBV, contraceptive practices must start on Study Day 1 and must continue for 30 days after stopping study drugs.

    For subjects whose study drug regimen will include RBV, the contraceptive practices must start on Study Day 1 and must continue for 7 months after stopping study drug, or **as directed by the local ribavirin label.**

    (Note: Estrogen-containing hormonal contraceptives, including oral, injectable, implantable, patch and ring varieties, may not be used during study drug treatment).

3. Females must have negative results (unless otherwise noted below) for pregnancy tests performed:

   - at Screening by serum specimen within 35 days prior to initial study drug administration, and
   - at Baseline (prior to dosing) by urine specimen

   Female subjects with a borderline human chorionic gonadotropin (hCG) result at Screening and/or Day 1 may enroll into the study if they either:

   - have a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy; or
   - are confirmed to be postmenopausal defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a FSH level indicating a postmenopausal state at Screening.

4. Males who are not surgically sterile who are sexually active with female partner(s) of childbearing potential, must agree to practice two effective forms of birth control (as outlined in the subject information and consent form or other subject information documents).

   For subjects whose study regimen includes RBV, the contraceptive practices must be observed from Study Day 1 and must continue for 7 months after stopping study drug, or as directed by the local RBV label.

   For subjects whose study regimen does not include RBV, these contraceptive practices must start on Study Day 1 and must continue until 30 days after stopping study drugs.

5. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements and must voluntarily sign and date an informed consent.

6. Body Mass Index (BMI) is from ≥ 18 to < 38 kg/m^2 at the time of screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).

7. Chronic HCV infection prior to study enrollment. Chronic HCV infection is defined as one of the following:

   - Positive for anti-HCV Antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
   - HCV RNA > 10,000 IU/mL at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrollment with evidence of chronic hepatitis C disease).

8. Screening laboratory results from the central laboratory indicating HCV genotype 3 infection only.

9. Absence of cirrhosis, as documented by meeting one of the following criteria (per local standard practice):

- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis;
- Only in the absence of a biopsy within the 24 months prior to screening or during screening:
  - a Screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or
  - a Screening transient elastography (e.g., FibroScan®) results of < 12.5 kPa.

Subjects with a FibroScan result that is ≥ 12.5 kPa and < 14.6 KPa, **or** a FibroTest result that is ≤ 0.72 and an APRI > 2, **or** a FibroTest result that is > 0.73 and an APRI ≤ 2 must have a liver biopsy performed within 24 months prior to screening showing no evidence of cirrhosis, or in the absence of an available biopsy result within 24 months prior to screening, may undergo a liver biopsy during screening to rule out cirrhosis. The result of the liver biopsy will be considered the decisive result for study eligibility and subjects may be enrolled as non-cirrhotic only if the biopsy performed within the previous 24 months or during the Screening period shows no evidence of cirrhosis.

Rationale for Inclusion Criteria

1, 7 – 9	To select the appropriate subject population with sufficient disease severity for evaluation
6	For the safety of study subjects
2 – 4	RBV has known teratogenic effects
5	In accordance with Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. Use of any herbal supplements (including milk thistle) within 2 weeks or 10 half-lives (if known) of the respective supplement, whichever is longer, prior to the first dosing of study drug.

2. Females who are pregnant or plan to become pregnant, or breastfeeding, or males whose partners are pregnant or planning to become pregnant within 7 months (or per local RBV label) after their last dose of study drug.
3. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.
4. Positive test result for Hepatitis B surface antigen (HbsAg) or anti HIV Ab positive.
5. HCV genotype performed during screening indicates co infection with any genotype other that genotype 3.
6. Use of known strong inducers of cytochrome P450 3A (CYP3A) or any strong inducers of P-glycoprotein (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) and any medications listed below, as well as those that are contraindicated for SOF, ritonavir or RBV, if applicable, within 2 weeks prior or 10 half-lives of the medication whichever is longer, to study drug administration including but not limited to:

Table 3. Medications Contraindicated for Use with the Study Drug Regimen

Alfuzosin	Ergot Derivatives	Quinidine
Alprazolam	Estazolam	Rifabutin
Amiodarone	Estrogen-containing medications for systemic use	Rifampin
Ampiroxicam	Flecainide	Rifapentine
Astemizole	Flurazepam	Rivaroxaban
Azelnidipine	Fusidic Acid	Salmeterol
Bepridil	Lovastatin	Sildenafil*
Blonanserin	Midazolam	Simvastatin
Carbamazepine	Oxcarbazepine	St. John's Wort
Cisapride	Phenobarbital	Tadalafil
Clorazepate	Phenytoin	Terfenadine
Diazepam	Pimozide	Triazolam
Efavirenz	Piroxicam	Vardenafil
Eletriptan	Propafenone	Voriconazole

* When used for the treatment of pulmonary arterial hypertension.

Note: Not all medications contraindicated with SOF, ritonavir and ribavirin are listed above. Refer to the most current package inserts or product labeling of ritonavir and ribavirin for a complete list of contraindicated medications.

7. Clinically significant abnormalities or co-morbidities, other than HCV infection that make the subject an unsuitable candidate for this study in the opinion of the investigator.
8. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
9. 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
- Drug-related liver disease

10. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks prior to study drug administration.

11. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ombitasvir, ABT-450, ritonavir, SOF, or RBV (if applicable).

12. Current enrollment in another clinical study, previous enrollment in this study, or previous use of any investigational or commercially available anti-HCV therapy (other than interferon, pegIFN, RBV, and/or SOF) including previous exposure to telaprevir, boceprevir, ABT-450, or ombitasvir (ABT-267). Subjects who previously participated in trials of investigational anti-HCV agents may be enrolled with the approval of the AbbVie Study Designated Physician if they can produce documentation that they received only placebo. Concurrent participation in a non-interventional, epidemiologic, or registry trial may be permitted with approval by the AbbVie Study Designated Physician.

13. Uncontrolled clinically significant cardiac, respiratory (except mild asthma), hepatic (except HCV-related disease), gastrointestinal, hematologic, or psychiatric disease or disorder, or any uncontrolled medical illness, which is unrelated to the hepatic disease.

14. History of solid organ transplant.

15. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir score > 3 or an Ishak score > 4.

16. Screening laboratory analyses showing any of the following abnormal laboratory results:

- Calculated creatinine clearance (using Cockcroft-Gault method) < 30 mL/min.

- Albumin < Lower limit of normal (LLN).
- Prothrombin time/International normalized ratio (INR) > 1.5. Subjects with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the AbbVie Study Designated Physician.
- Hemoglobin < LLN.
- Platelets < 120,000 cells per mm^3.
- Absolute neutrophil count (ANC) < 1500 cells/µL (< 1200 cells/µL for subjects of African descent who are black).
- Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN.

Rationale for Exclusion Criteria

1, 3, 5, 10, 12	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medication
2, 6 – 8, 11, 13 – 16	To ensure safety of the subjects throughout the study
4, 9	To exclude subjects with liver diseases other than HCV

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded 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 PT Period, all medications will be recorded until 30 days following the last dose of study drugs. Only medications associated with HCV treatment will be collected thereafter.

The AbbVie Study Designated Physician should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior HCV Therapy

Subjects may have previously received prior interferon, pegIFN, RBV, and/or SOF treatment and failed treatment (either on treatment or via relapse post-treatment). All available documentation of prior treatment history, including start and stop dates and HCV RNA levels, should be collected in the source to document the type of non-response.

Subjects must have discontinued prior therapy at least 2 months prior to the Screening Visit in order to be eligible for the study.

Prior or current use of any other investigational or commercially available anti-HCV agents other than interferon, pegIFN, RBV, and/or SOF, excludes a subject from this study. Subjects who previously participated in trials of investigational anti-HCV agents may be enrolled if they can provide documentation that they received only placebo.

5.2.3.2 Concomitant Therapy

Subjects must be able to safely discontinue any prohibited medications or herbal supplements within 2 weeks or within 10 half-lives of the respective medication/supplement (if known), whichever is longer, prior to initial study drug administration and through 2 weeks following discontinuation of study drugs. Subjects must be consented prior to discontinuing any prohibited medications or herbal supplements for the purpose of meeting study inclusion criteria.

The investigator should confirm that concomitant medication can be safely administered with DAAs (including ritonavir) and RBV, if applicable. Some medications may require dose adjustments due to potential for drug-drug interactions. Subjects should be on a stable dose of concomitant medications for at least 2 weeks prior to initiation of study drug. The investigator can also review the label(s) for the concomitant medication(s) for additional information.

During the PT Period, investigators should reassess concomitant medications and subjects may resume previously prohibited medications, or revert to pre-study doses, 2 weeks following discontinuation of study drugs, if applicable.

Influenza vaccinations and all essential vaccinations in this subject population are allowed during Screening through the PT Period.

5.2.3.3 Prohibited Therapy

Subjects must be able to safely discontinue any prohibited medications within 2 weeks or within 10 half-lives of the respective medication/supplement (if known), whichever is longer, prior to initial study drug administration through 2 weeks following discontinuation of study drugs. Subjects must be consented prior to discontinuing any prohibited medications for the purpose of meeting study inclusion criteria.

In addition to the medications listed in Table 3, use of known strong inducers of CYP3A or strong inhibitors or inducers of P-glycoprotein is prohibited within 2 weeks of the respective medication/supplement prior to the initial dose of study drug through the first 2 weeks after the subject has completed study drugs.

Refer to the current local labels for ritonavir, RBV, and SOF for a list of prohibited medications. Anti-HCV medications other than those specified in the protocol will not be allowed during the treatment period of the study.

Contraceptives

Prior to enrollment, subjects should agree to practice two effective methods of birth control while receiving study drugs starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. Subjects using systemic estrogen-containing contraceptive therapy (including estrogen-containing oral contraceptives) have a higher risk for elevated ALT levels. Subjects using these medications must discontinue them at least 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer. Subjects may replace the systemic

estrogen-containing contraceptive with a progestin-only hormonal contraceptive method. Estrogen-containing contraceptives may be resumed 2 weeks after the last dose of DAAs.

Use of hematopoietic growth factors is not permitted during this study without the approval of the AbbVie Study Designated Physician. 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.

5.3 Efficacy Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described in this protocol are summarized in Table 4 and Table 5.

Table 4. Study Activities – Treatment Period

Activity	Screening[a]	Day 1/ Baseline[b]	Wk 1	Wk 2	Wk 4	Wk 8	Wk 10	Wk 12 (EOT)	Premature D/C Treatment[c]
Informed Consent	X								
Provide RBV Medication Guide[d]	X								
Medical History	X	X[e]							
Physical Exam	X	X						X	X
Vital Signs, Weight, Height[f]	X	X	X	X	X	X	X	X	X
ECG[g]	X							X	X
Hematology/Chemistry/Urinalysis/Coagulation Panel	X	X	X	X	X	X	X	X	X
Pregnancy Test (serum [s] urine [u])[h]	X (s)	X (u, s)			X (u)	X (u)		X (u)	X (u)
FSH (all females)	X								
HBsAg, Anti-HCV Ab, Anti HIV Ab	X								
HgbA1c	X								
HCV Genotype and Subtype	X								
Liver Biopsy or FibroTest or FibroScan®[i]	X								
IL28B Sample	X								
Pharmacogenetic Sample (Optional)[j]		X							
Messenger RNA (mRNA) Sample (Optional)		X		X				X	X
Total Insulin		X						X	X

Table 4. Study Activities – Treatment Period (Continued)

Activity	Screening[a]	Day 1/ Baseline[b]	Wk 1	Wk 2	Wk 4	Wk 8	Wk 10	Wk 12 (EOT)	Premature D/C Treatment[c]
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X[k]	X	X	X	X	X	X	X	X
Patient Report Outcomes Instruments (PROs)[l]		X			X	X		X	X
Study Drugs Dispensed		X			X	X			
Study Drugs Collected and Compliance Reconciled in IRT					X	X		X	X
HCV RNA Samples	X	X	X	X	X	X	X	X	X
HCV Resistance Sample		X	X	X	X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X	X	X	X
Archive Serum Sample	X	X	X	X	X	X	X	X	X
Pharmacokinetic Samples[m]		X	X	X	X	X	X	X	X
Interferon Gamma-Induced Protein 10 (IP-10) Sample		X			X	X		X	X

EOT = End of treatment; D/C = Discontinuation

a. A signed study-specific informed consent will be obtained from the subject (with proper source documentation reflecting this process) before any study procedures are performed at the Screening Visit.

b. All procedures will be performed prior to first dose.

c. All subjects should begin PT Period after the subject prematurely discontinues study drugs treatment in this period.

d. Where applicable/locally available.

e. The medical history will be updated at the Day 1 Visit. This updated medical history will serve as the Baseline for clinical assessment.

f. Height will be measured at the Screening Visit only.

Table 4. Study Activities – Treatment Period (Continued)

g. Evaluate the Screening ECG prior to dosing to determine eligibility.

h. Urine pregnancy test is not required after the Day 1 Visit for female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy or who are confirmed to be post-menopausal. A positive urine pregnancy test requires a confirmatory serum test.

i. For subjects who have not had a qualifying liver biopsy within the previous 24 months.

j. If the optional pharmacogenetic sample is not collected at Study Day 1, it may be collected at any other visit during the study. Verify subject has given consent to pharmacogenetic testing.

k. Protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent until study drug administration.

l. EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) and Fatigue Severity Scale (FSS) should be administered before any study procedures and in the order listed.

m. PK samples will be collected at 2, 4, and 6 hours post-DAA dose at Day 1. Additional intensive PK samples will be collected at the Week 2 study visit where samples will be collected at pre-dose and approximately 2, 4, and 6 hours post-DAA dose. On the day of intensive blood sampling, subjects will take their morning dose of DAAs and ribavirin onsite in the presence of study site personnel and the time of administration will be recorded to the nearest minute.

Table 5. Study Activities – Post-Treatment (PT) Period

Activity	PT Wk 2	PT Wk 4	PT Wk 8	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48 or PT D/C
Vital Signs and Weight	X	X	X	X	X	X	X
Hematology/Chemistry/Urinalysis/Coagulation Panel		X		X			
Monthly Pregnancy Test (females)[a]		X	X	(Weeks 12, 16, 20, 24, 28)			
PRO Instruments[b]		X		X	X		X
Concomitant Medication Assessment[c]	X	X	X	X	X	X	X
Adverse Event Assessment[d]	X	X					
HCV RNA Samples	X	X	X	X	X	X	X
HCV Resistance Sample	X	X	X	X	X	X	X
Archive Plasma Sample	X	X	X	X	X	X	X
Archive Serum Sample	X	X	X	X	X	X	X
IP-10 Sample					X		X
mRNA Sample (Optional)	X			X			

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

a. Urine pregnancy testing is not required after the Day 1 Visit for female subjects with a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy, or who are confirmed post-menopausal. For subjects on a RBV-inclusive regimen, 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 at PT Weeks 16, 20 and 28. Additional testing may be required per local RBV label.

b. EuroQol5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) and Fatigue Severity Scale (FSS) should be administered before any study procedures and in the order listed.

Table 5. Study Activities – Post-Treatment (PT) Period (Continued)

c. Only medications related to the treatment of HCV will be collected after 30 days post-dosing.

d. Adverse events and serious adverse events will be collected until 30 days post-dosing.

Note: Day 1 of the PT Period will be defined as the day after the last dose of active study drug treatment.

5.3.1.1 Study Procedures

The study procedures outline in Table 4 and Table 5 are discussed in detail in this section, with the exception of the assessment of concomitant medications (Section 5.2.3.2), the monitoring of treatment compliance (Section 5.5.6), the collection of adverse event information (Section 6.4), the collection of the IL28B sample (Section 5.3.1.3), the collection of blood samples for the optional pharmacogenetic analysis (Section 5.3.1.3), and the collection of blood samples for pharmacokinetic analysis (Section 5.3.2). All study data will be recorded in the subject's source documentation and then on the appropriate eCRFs, with the exception of central laboratory data which will be provided to AbbVie electronically from the individual laboratory(ies).

Informed Consent and RBV Information

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. Subjects on a RBV-inclusive regimen will be given the RBV Medication Guide (where applicable/locally available). Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical History

A complete medical history, including history of tobacco and alcohol, will be taken from each subject during the Screening Visit. The subject's medical history will be updated 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 Table 4 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.

Vital Signs, Weight, Height

Body temperature (oral or tympanic), blood pressure, pulse, and body weight will be measured at the visits indicated in Table 4 and Table 5. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The subject should wear lightweight clothing and no shoes during weighing. Height will only be measured at Screening; the subject will not wear shoes.

12-Lead Electrocardiogram

A 12-lead resting ECG will be obtained at visits specified in Table 4 (or as clinically needed). The ECG will be obtained prior to the blood collection.

ECGs will be recorded after the subject has been supine for at least 5 minutes. Subjects should be instructed to remain completely stationary during the ECG recording (approximately 10 seconds), with no talking, laughing, deep breathing, sleeping, or swallowing.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will interpret, sign, and date all ECG tracings and will provide his/her global interpretation as a written commitment 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. The QT interval measurement (corrected by Fridericia's formula, QTcF) will be documented in the eCRF only if the local reader selects "prolonged QT" on the eCRF.

The original ECG tracing will be retained in the subject's record at the study site.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 6 at the visits specified in Table 4 and Table 5. Blood samples for serum chemistry tests should ideally be collected following a minimum 8-hour fast (with the exception of the Screening Visit, which may be done non-fasting). Subjects whose visits occur prior to the morning dose of study drugs should be instructed to fast after midnight. Subjects whose visits occur following the morning dose of study drugs should be instructed to fast after breakfast until the study visit occurs. Blood samples should still be drawn if the subject did not fast for at least 8 hours. 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 drugs.

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

Sites should refer to the laboratory manual provided by the central laboratory, AbbVie, or its designee for instructions regarding the collection, processing, and shipping of all laboratory samples.

The certified laboratory chosen for this study is Covance. Depending on the location of the study site, samples will be sent to one of the following addresses:

For sites in the Canada and USA:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA

For sites in the United Kingdom:

Covance
7 rue Marcinhes
1217 Geneva
Meyrin Switzerland

For sites in Australia and New Zealand:

Covance (Asia) Pte Ltd.
1 International Business Park
#01-01 The Synergy
Singapore 609917

Table 6. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) ANC Prothrombin Time/INR Activated partial thromboplastin time (aPTT) Reticulocyte count	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin[a] Direct and indirect bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin Chloride Bicarbonate Magnesium Gamma-glutamyl transferase (GGT)[a] Creatinine clearance (Cockcroft-Gault calculation) Alpha2-macroglobulin[a,b] Haptoglobin[a,b] Apolipoprotein A1[a,b]	Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Microscopic (reflex) Albumin **Additional Tests** HBsAg Anti-HCV Ab[c] Anti-HIV Ab[c] FSH (females)[c] Urine and Serum Human Chorionic Gonadotropin (hCG) (females)[d] Total insulin HCV RNA Hemoglobin A1C[c] IP-10 IL28B[c] HCV genotype and subtype[c] Pharmacogenetic sample (optional) mRNA sample (optional)

a. Component of FibroTest.

b. Performed only during Screening Period for FibroTest, if needed.

c. Performed only at Screening.

d. Urine pregnancy testing is not required after Day 1 for female subjects who are confirmed to be post-menopausal or who have a documented history of prior bilateral tubal ligation, bilateral oophorectomy or hysterectomy.

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

- The investigator will repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.

- A laboratory test value that requires a subject to be discontinued from the study or study drugs or requires a subject to receive treatment that will be recorded as an adverse event.

The management of laboratory abnormalities that may occur during the study is described in Section 6.7.

Pregnancy Test

A urine pregnancy test will be performed for all female subjects at all visits specified in Table 4 and Table 5. In addition, a serum pregnancy test will be performed at Screening and Study Day 1 Visits and analyzed by the central laboratory. All urine pregnancy tests will be performed on-site during the study visit if there is a scheduled visit, as specified in Table 4 and Table 5. A positive urine pregnancy test requires a confirmatory serum test. Urine pregnancy tests are not required after Day 1 for female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or for subjects who are confirmed to be postmenopausal. Confirmation of postmenopausal status will be determined during the Screening period, based on the subject's history, and measured by FSH.

For subjects on a RBV-inclusive regimen where there is not a scheduled study visit, female subjects of childbearing potential may either have PT Period pregnancy testing performed at the site as an unscheduled visit using an unscheduled visit test kit or a urine pregnancy test may be conducted by the subject at home with a pregnancy test kit provided by the site; site personnel should contact these female subjects to capture the results of any study-related pregnancy tests performed at home. The pregnancy test results will only be recorded in the subject's source records.

If the subject elects to return to the study site for an unscheduled visit for pregnancy testing, the results of the urine pregnancy test will be recorded on the eCRF, unless serum pregnancy test is elected. Serum pregnancy testing will be completed by the central laboratory and loaded into the clinical database.

Hepatitis and HIV Screen

HBsAg, anti-HCV Ab, 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 HBV HBsAg results will be reported by the central laboratory to the clinical database.

HCV Genotype and Subtype

Plasma samples for HCV genotype and subtype will be collected at Screening. Genotype will be assessed using the Versant® HCV Genotype Inno-LiPA Assay, version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY).

Liver Diagnostic Testing

FibroTest/APRI and FibroScan are non-invasive measurements of liver fibrosis that have shown good correlation with liver biopsy on predicting the presence of significant fibrosis or cirrhosis.

The identification of cirrhosis on an appropriately performed and reported liver biopsy at any prior time point is considered sufficient and definitive evidence to establish the presence of cirrhosis.

Subjects who have not had a liver biopsy within previous 24 months and who have not a biopsy establishing cirrhosis at any time prior to 24 months but who otherwise meet all of the inclusion criteria and none of exclusion criteria will undergo liver biopsy or **one** non-invasive test (FibroTest/APRI or FibroScan) prior to enrollment. Selection of whether liver biopsy or one of the non-invasive tests should be performed will be based on local standard practice.

For subjects with a FibroScan result that is ≥ 12.5 kPa and < 14.6 kPa; **or** a FibroTest result that is ≤ 0.72 and an APRI > 2; **or** a FibroTest result that is ≥ 0.73 and an APRI ≤ 2, the subject must have a liver biopsy performed within 24 months prior to screening, or in

the absence of an available biopsy result within 24 months of Screening, may undergo a liver biopsy during Screening to rule out cirrhosis.

Patient Reported Outcomes (PRO) Instruments (Questionnaires)

Subjects will complete the self-administered PRO instruments (where allowed per local regulatory guidelines) on the study days specified in Table 4 and Table 5. Subjects will be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaires to them. Site personnel will encourage completion of each instrument at all visits and will ensure that a response is entered for all items.

In this study, PRO instruments should be consistently presented so that subjects complete the EQ-5D-5L first and then the FSS. PRO instruments should be completed prior to drug administration on Day 1 and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

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

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

Fatigue Severity Scale (FSS) Instrument

The FSS measures the impact of fatigue over the past week on specific types of functioning (e.g., motivation, exercise, physical functioning, carrying out duties, interfering with work, family, or social life). The survey consists of 9 questions using a

7-point Likert scale. A total score is calculated as the average of the individual item responses. The scale's psychometric properties have been confirmed in chronic hepatitis C and other diseases. Subjects also rate their perception of their fatigue on a separate visual analogue fatigue scale (VAFS). The FSS should require approximately 5 minutes to complete.

Randomization and Assignment of Subject Numbers

All screening activities must be completed and reviewed prior to subject randomization. Screening numbers will be unique 4-digit numbers and will begin with 1001, with the first two digits representing the investigative site and the last two digits representing the subjects at the site. Enrolled subjects will keep their screening number as their subject number. Subjects who meet the eligibility criteria may proceed to randomization via the IRT system at the Study Day 1 Visit.

Randomized subjects will keep their screening number as their subject number. Subjects will be randomized on Day 1 as described in Section 5.5.3 and will receive a separate unique randomization number that will be recorded automatically in the eCRF through the IRT system. The randomization number will be used only by the Sponsor for loading the treatment schedule into the database.

HCV RNA Samples

Plasma samples for HCV RNA levels will be collected as indicated in Table 4 and Table 5. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0. The lower limit of detection (LLOD) is 20 IU/mL and results below LLOD are reported as "HCV RNA not detected;" the LLOQ for this assay is 25 IU/mL and results below LLOQ, but detectable are reported as "< 25 IU/mL HCV RNA detected."

HCV Resistance Testing Sample

A plasma sample for HCV resistance testing will be collected at the study visits indicated in Table 4 and Table 5.

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

Archive Plasma and Serum Sample

Archive plasma and serum samples will be collected at the study visits indicated in Table 4 and Table 5. Archive plasma and serum samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by AbbVie.

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

Interferon Gamma-Induced Protein 10 (IP-10) Levels

A plasma sample for IP-10 testing will be collected at the study visits indicated in Table 4 and Table 5. The IP-10 testing is exploratory and may not be provided to the investigator.

5.3.1.2 Meal and Dietary Requirements

All study drugs should be dosed together and administered with food, i.e., the AM dose of ombitasvir/ABT-450/r and SOF and, if applicable, RBV should be taken together with food and, if applicable, the PM dose of RBV should be taken together with food.

It is recommended that subjects avoid consumption of alcohol within the 72-hour period prior to any study drug administration and throughout the duration of the study.

5.3.1.3 Blood Samples for Pharmacogenetic Analysis

IL28B Samples

One (required) 2 mL whole blood sample for Deoxyribonucleic acid (DNA) isolation will be collected from each subject at Screening for Interleukin 28B (IL28B) pharmacogenetic analysis. The sample will not be used for any testing other than IL28B genotypes. IL28B genotyping will be performed by the central laboratory.

Blood Samples for Pharmacogenetic Analysis (Optional)

One 4 mL whole blood sample for DNA isolation will be collected on Day 1 from each subject who consents to provide a sample for pharmacogenetic analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3. If the sample is not collected on Day 1, it may be collected at any time throughout the study.

The sample collection tubes will minimally be labeled with "PG-DNA," protocol number, and subject number. Samples will be shipped frozen to AbbVie or a designated laboratory for DNA extraction and long-term storage. Instructions for the preparation and shipment of pharmacogenetic samples will be provided in the lab manual.

AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-450/ombitasvir (or drugs of this class) continues but no longer than 20 years.

Blood Samples for Messenger RNA (mRNA) Analysis (Optional)

Separate optional whole blood samples will be collected from those subjects who choose to participate and consent to additional mRNA analysis. The procedure for obtaining and documenting informed consent for this optional sample is discussed in Section 9.3.

Subjects who consent to participate in the mRNA substudy will have blood samples taken as indicated in Table 4 and Table 5.

Messenger RNA levels related to HCV disease or response to drug therapy will be measured in peripheral whole blood. For biomarker analysis, mRNA expression may be analyzed using microarray and polymerase chain reaction (PCR) technique in peripheral blood samples. This analysis will measure the levels of essentially all mRNAs present in the collected peripheral blood samples.

Results of mRNA testing are considered exploratory and may not be included in the Clinical Study Report.

The optional blood samples for mRNA must be collected at visits specified in Table 4 and Table 5. Samples will be shipped frozen to AbbVie or a designated laboratory for RNA extraction and long-term storage.

Samples will be stored in a secure storage space with adequate measures to protect confidentiality. These samples will be retained while research on ombitasvir and ABT-450 or drugs of these classes continues, but no longer than 20 years.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for assay of ombitasvir, possible ombitasvir metabolites, ABT-450, possible ABT-450 metabolites, ritonavir, SOF, GS-331007 (predominant circulating metabolite of SOF), and RBV (if applicable) will be collected by venipuncture at each study visit specified in Table 4 (irrespective of study drug dosing time). Actual times of dosing for the last dose and second to the last dose will be recorded on the applicable requisition forms and in the eCFR, and accordingly, time after dose for pharmacokinetic sample collection will be determined.

Intensive pharmacokinetic samples will be collected on Day 1 at 2, 4, and 6 hours post-DAA dose and at the 2-week visit at predose and approximately 2, 4, and 6 hours post-DAA dose. The time that each blood sample is collected will be recorded to the nearest minute on the subject dosing card and in the eCRF.

At each planned collection time, two blood samples will be collected (one 4 mL sample intended for DAA/RBV analysis and one 4 mL sample intended for SOF/GS-331007 analysis).

Approximately 12 DAA/RBV and 12 SOF/GS-331007 blood samples are planned to be collected per subject during 12 weeks of treatment for pharmacokinetic analysis. At minimum, the total number of samples planned for pharmacokinetic analysis is 480 for the entire study.

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 pharmacokinetic assays of ombitasvir, possible ombitasvir metabolites, ABT-450, possible ABT-450 metabolites, SOF, GS-331007, ritonavir, and RBV (if applicable) will be provided by the central laboratory, AbbVie, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of ombitasvir, possible ombitasvir metabolites, ABT-450, possible ABT-450 metabolites, ritonavir, SOF, GS-331007, RBV (if applicable), and archive plasma samples will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

The central laboratory will then ship samples for the pharmacokinetic assays of ombitasvir, possible ombitasvir metabolites, ABT-450, possible ABT 450 metabolites, and RBV to:

Sample Receiving
[redacted]
c/o: Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL 60085

[redacted]

An inventory of the samples included will accompany the package and an electronic copy of the Manifests (including subject number, study day, the time of sample collection, and barcode) will be sent to the contact person at sample.receiving@abbvie.com.

The central laboratory will then ship samples for the pharmacokinetic assays of SOF, GS-331007, and other possible metabolites of SOF to reference laboratories following separately provided instructions.

An inventory of the SOF samples included will accompany the package and an electronic copy of the Manifests (including subject number, study day, and the time of sample collection) will be sent to [redacted].

5.3.2.4 Measurement Methods

The plasma concentration of ombitasvir, ABT-450, ritonavir, SOF, GS-331007 (predominant circulating metabolite of SOF), and RBV (if applicable), will be analyzed using validated assay methods under the supervision of the Drug Analysis Department at AbbVie. Plasma concentrations of possible metabolites of ombitasvir, ABT-450, and SOF (other than GS-331007) may also be determined using either validated or non-validated methods.

5.3.3 Efficacy Variables

Virologic response will be assessed by HCV RNA in IU/mL at various time points from Day 1 through 48 weeks after completion of treatment.

5.3.3.1 Primary Variable

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

5.3.3.2 Secondary Variable

The secondary endpoints are:

- The percentage of subjects with virologic failure during treatment;
- The percentage of subjects with post-treatment relapse.

5.3.4 HCV Resistance Variables

The following resistance information will be provided for all subjects: the amino acid variants at baseline at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence.

The following resistance information will be analyzed for subjects 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 population and/or clonal nucleotide sequencing and comparison to the baseline sequence, 2) the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence, and 3) the persistence of resistance-associated amino acid variants by population and/or clonal nucleotide sequencing during the post-treatment period.

5.3.5 Safety Variables

The following safety evaluations will be analyzed during the study: adverse event monitoring and vital signs, physical examination, and laboratory test assessments.

5.3.6 Pharmacokinetic Variables

Plasma samples for ombitasvir, ABT-450, ritonavir, SOF, GS-331007 (predominant circulating metabolite of SOF), and RBV (if applicable) will be collected at each study visit up to 12 weeks. Individual plasma concentrations of possible metabolites of ombitasvir and ABT-450 may be measured and summarized if they are needed for additional safety or efficacy evaluation.

Values for the pharmacokinetic parameters of ombitasvir, ABT-450, ritonavir, SOF, GS-331007 (predominant circulating metabolite of SOF), and RBV (if applicable) including the C_{max}, T_{max}, C_{trough}, and AUC will be determined by noncompartmental methods using intensive pharmacokinetic blood sampling data in the study. Additional parameters or summaries may be determined if useful in the interpretation of the data.

5.3.7 Pharmacogenetic Variables

IL28B genotypes are associated with response to pegIFN and RBV and to some pegIFN-free regimens. IL28B status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. These IL28B genotype results may be analyzed as part of a multi-study assessment of IL28B and response to ombitasvir, ABT-450, and SOF.

DNA samples from subjects who separately consent for additional pharmacogenetic analysis may be sequenced and data analyzed for genetic factors contributing to the disease or subject's response to ombitasvir/ABT-450, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, other genes believed to be related to the disease or to drug response (including IL28B). Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ombitasvir/ABT-450, drugs of this class, or the disease state. The samples may also be used for the development of diagnostic tests related to ombitasvir/ABT-450 and SOF,

drugs of these classes, or the disease state. The results of pharmacogenetic analyses may not be reported with the study summary.

Messenger RNA samples from subjects who separately consent for the mRNA substudy may be analyzed for RNA expression levels contributing to the subject's response to study treatment in terms of pharmacokinetics, pharmacodynamics, efficacy, tolerability and safety. Analysis may include quantifying RNA levels from interferon-stimulated pathways or other families believed to be related to drug response. Messenger RNA analysis will be limited to studying response to HCV therapy; no other analyses will be performed.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from treatment or the study at any time. In addition, the investigator may discontinue a subject from treatment or 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 treatment, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 4. It is recommended that this visit occur on the day of study drug discontinuation; however, this visit should occur within 2 days following their final dose of study drugs 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 conditions. Following discontinuation of study drugs, the subject will be treated in accordance with the investigator's best clinical judgment. The date of the last dose of study drug and reason for discontinuation will be recorded in the eCRF. The subject should then begin the PT Period where the subject will be monitored for 48 weeks for safety, HCV RNA, the emergence and persistence of resistant viral variants, and assessments of PROs.

If a subject discontinues from the PT Period, the subject should return for post-treatment discontinuation procedures defined in Table 5. The reason for discontinuation will also be recorded in the eCRF.

If a subject is discontinued from study drug (Treatment Period) or the PT Period with an ongoing adverse event or an unresolved laboratory result that is significantly outside 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 (Section 6.7). Subjects receiving a RBV-inclusive regimen who report a positive result is obtained on a pregnancy test during the Treatment Period must be notified to stop RBV immediately. Administration of DAAs may be continued at the investigator's discretion, if the benefit of continuing therapy is felt to outweigh the risk. Specific instructions regarding subject pregnancy can be found in Section 6.6. Subjects will continue to be monitored for SVR in the PT Period as described in Section 5.1.3. If the subject is receiving a RBV-containing regimen, the investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry.

5.4.1.1 Virologic Failure Criteria for Subject Management

The following criteria will be considered evidence of virologic failure leading to discontinuation of study drug while receiving study drug and will be discontinued from study drug:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment; or
- Failure to achieve HCV RNA < LLOQ by Week 8; or
- Confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA ≤ LLOQ.

Confirmatory testing should be completed as soon as possible. Subjects should remain on study drug treatment until the virologic failure has been confirmed. If any of the above criteria are met, the subject will discontinue study drug treatment (Section 5.4.1).

Subjects with HCV RNA < LLOQ at the end of treatment and who have a confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point in the PT Period will be considered to have relapsed. Confirmation of an HCV RNA ≥ LLOQ in the PT Period should be completed as soon as possible per Section 5.1.3.

5.4.1.2 Safety Stopping Criteria

Enrollment in any treatment arm may be discontinued at any time by the AbbVie Study Designated Physician if ongoing data review reveals a potential risk to subject safety. Treatment arms may also be dropped prior to initiation of the study based on available safety data from ongoing studies.

Depending on the nature and severity of the triggering safety event(s), subjects already enrolled in the affected arm(s) might continue to receive study treatment, or subjects might discontinue all study drug dosing. In the latter case, subjects may be offered another off-study (non-AbbVie) treatment regimen, as determined appropriate by the investigator.

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 DAA study drugs (ombitasvir/ABT-450/r and SOF) and RBV (if applicable) will be dispensed in the form of tablets. Study drugs will be dispensed at the visits listed in Table 4.

Ombitasvir/ABT-450/r will be provided by AbbVie as 12.5 mg/75 mg/50 mg tablets. Ombitasvir/ABT-450/r will be taken orally as 2 tablets every morning which corresponds to a 25 mg ombitasvir/150 mg ABT-450/100 mg ritonavir dose QD.

SOF will be provided by AbbVie as 400 mg tablets. SOF will be taken orally as 1 tablet every morning, which corresponds to a 400 mg dose QD.

For subjects randomized to a RBV-inclusive regimen, RBV will be provided as 200 mg tablets during the Treatment Period. RBV should be dosed based on consideration of the subject's weight from Study Day 1, either 1000 mg or 1200 mg daily divided BID per local label (e.g., < 75 kg = 1000 mg daily divided BID or ≥ 75 kg = 1200 mg daily divided BID) and his/her hemoglobin test results from the Screening Visit, according to the current approved local RBV label.

For subjects with calculated creatinine clearance ≥ 30 to < 50 mL/min, RBV should be given as alternating daily doses of 200 mg and 400 mg as described in Section 6.7.6; Table 9. Subjects will be instructed to take study medication at the same time(s) every day. All study drugs should be administered with food. Subjects will be instructed to bring in all bottles at each visit.

Following enrollment, the site will use the IRT system to obtain the study drug container numbers to dispense at the study visits specified in Table 4. Study drugs must not be dispensed without contacting the IRT system, and only for subjects enrolled in the study through the IRT system. The site will also contact the IRT system to provide study drug return information for each container at the visits specified in Table 4 (Section 5.5.7).

At Study Day 1, subjects will be administered study drugs by the study site personnel and receive instructions for self-administration of all study drugs from Study Day 2 through the end of the Treatment Period.

All subjects who receive at least one dose of DAA who meet virologic failure criteria during treatment (Section 5.4.1.1) will be discontinued from treatment. Resistance monitoring will continue in the PT Period regardless of whether subjects opt for alternative post-study treatment.

5.5.2 Identity of Investigational Product

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

Table 7. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
ombitasvir/ABT-450/ ritonavir	AbbVie	Oral	Tablet	12.5 mg/75 mg/ 50 mg
sofosbuvir	Gilead Sciences Inc.	Oral	Tablet	400 mg
ribavirin	Roche or generic manufacturer	Oral	Tablet	200 mg

5.5.2.1 Packaging and Labeling

Ombitasvir/ABT-450/ritonavir will be supplied in bottles containing 64 tablets. Sofosbuvir will be supplied in bottles containing 28 tablets. Ribavirin, if applicable, will be supplied in bottles containing 168 tablets each.

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
ombitasvir/ABT-450/ritonavir bottles	15° to 25°C (59° to 77°F) Australia and New Zealand: Store below 25°C
ribavirin bottles	15° to 25°C (59° to 77°F) Australia and New Zealand: Store below 25°C
sofosbuvir bottles	15° to 25°C (59° to 77°F) and protect from moisture Australia and New Zealand: Store below 25°C and protect from moisture

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. Upon receipt of study drugs, the site will acknowledge receipt within the IRT system.

5.5.3 Method of Assigning Subjects to Treatment Arms

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

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

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

5.5.4 Selection and Timing of Dose for Each Subject

Study drug dosing will be initiated at the Study Day 1 Visit. Ombitasvir/ABT-450/r and SOF will be dosed QD. Thus with normal dosing, 2 ombitasvir/ABT-450/r tablets and 1 SOF tablet should be taken in the morning.

RBV (if applicable) should be dosed BID, e.g., 2 or 3 tablets taken in the morning, and 3 RBV tablets should be taken in the evening. Subjects with renal impairment should receive a reduced dose of RBV, as described below (Table 8).

Table 8. Recommended Ribavirin Dosing in Chronically HCV-Infected Patients with Chronic Kidney Disease

Renal Impairment and Creatinine Clearance, mL/min	Renal Severity	RBV Dose (mg/day)
Normal (> 80 mL/min)	None	1000/1200
CKD Stage 3 (30 – 50 mL/min)	Moderate	200 alternating with 400
CKD Stage 4 (< 30 mL/min)	Severe	200

Note: Brennan et al.[25]

All study drugs should be dosed together and administered with food.

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. All study drugs will be dispensed to study subjects by study-site personnel under the direction of the investigator.

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. Subjects will be administered study drugs at the site at the Day 1 Visit. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs.

Subjects will be instructed to bring all study drug containers of ombitasvir/ABT-450/r and SOF and, when relevant, RBV (full, partial or empty) to the study site at each visit indicated in Table 4. Study site personnel will inspect the contents of the containers and record the exact number of remaining tablets of ombitasvir/ABT-450/r and SOF and, when relevant, tablets of RBV. Reconciliation in IRT should occur only when the container is returned to the site at the reconciliation visits indicated in Table 4. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

At the Day 1 visit, the date and time of the first dose of all drugs (i.e., first dose of first drug) will be recorded in the source documents and the eCRF. The date of last dose of all study drugs (i.e., last dose of last drug) will be recorded in the source documents and the appropriate eCRF. Subjects will be given dosing cards to record the last 2 doses of all study drugs prior to each study visit during the treatment period.

Study drugs should not be interrupted for toxicity management or any other reason for more than 7 days consecutively. If study drugs need to be interrupted for more than 7 days consecutively, the AbbVie Study Designated Physician should be contacted and consideration should be given to discontinue the subject.

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 drugs will be kept by the investigator and will include shipping invoices and date dispensed for each subject. An overall accountability of the study drugs will be performed and verified by the AbbVie monitor

throughout the Treatment Period. Final accountability will be performed 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 container, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the containers are damaged, the subject will be requested to return the remaining study drugs to the site. Replacement study drugs may only be dispensed to the subject by contacting the IRT system. Study drug replacement and an explanation of the reason for the misplaced or damaged study drug container will be documented within the IRT system. Study drug start/end dates will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each container, number of tablets remaining in each one returned and the date of reconciliation will be documented in the IRT system. The monitor will review study drug accountability periodically throughout the study.

Upon completion of or discontinuation from the Treatment Period, all original containers (containing unused study drugs) will be destroyed on site where possible or returned to AbbVie (or designee). All empty bottles should be destroyed on site. All destruction procedures will be according to instructions from AbbVie and according to local regulations following completion of drug accountability procedures. The number of tablets of each type of study drug returned in each container will be noted in the IRT system. 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 Arms

This study is an open-label pilot study designed to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of ombitasvir/ABT-450/r dosed in combination with SOF with or without RBV. The study will also provide information on the role of RBV with this regimen, the pharmacokinetics of ombitasvir/ABT-450/r and SOF with or without RBV in HCV-infected subject, the proportion of subjects achieving SVR_{12}, and the development and persistence of viral resistance with this treatment regimen.

High SVR rates have been reported in subjects with HCV genotype 3 infection treated with the combination of SOF and daclatasvir, another NS5A inhibitor, for 24 weeks.[23] Due to the presence of a third active agent, ABT-450, the treatment regimen in the current study is expected to have greater activity than that seen with SOF and daclatasvir; thus a greater treatment response is anticipated. The treatment duration for this study was selected based upon viral load modeling and simulations. Data for ABT-450/r + ombitasvir ± RBV in HCV genotype 3-infected subjects enrolled into Study [redacted] were modeled, as well as data for [redacted]. Since [redacted] in vitro potency is similar between genotypes 1 and 3, genotype 1 parameters were used to simulate the response in subjects infected with HCV genotype 3 infection. SVR for the combination of ABT-450/r + ombitasvir + SOF ± RBV was simulated using model parameters from the [redacted] analyses. Based upon these simulations, > [redacted]% of subjects receiving 2DAA + SOF ± RBV for 12 weeks are predicted to achieve SVR_{12} while treatment durations less than 12 weeks are predicted to result in a greater number of relapses. Hence, 12 weeks of dosing is planned.

The total daily dose of ombitasvir/ABT-450/r administered in this study has been administered to over 2000 HCV genotype 1-infected subjects, most often in combination with the non-nucleoside NS5B inhibitor dasabuvir for up to 24 weeks, and has been shown to be safe and well tolerated. Doses of both ABT-450/r and ombitasvir used in this study have both shown significant antiviral activity against genotype 1 HCV, and similar doses have shown activity against genotype 3 HCV (Study M12-998). Preliminary findings when ombitasvir/ABT-450/r and SOF were co-administered to healthy volunteers (Study M14-527) suggest that the combination is well tolerated, and based on the known metabolic and excretion pathways of the individual agents, no significant drug-drug interaction is anticipated; therefore, no dose adjustment for either component is expected to achieve exposures predicted to have optimal antiviral activity when compared to the individual compounds dosed singly. Ombitasvir/ABT-450/r and SOF dosing will not begin in this study until preliminary pharmacokinetic results from Study M14-527 are available to confirm absence of clinically meaningful drug-drug interactions.

The primary endpoint of this study is to assess the rate of SVR_{12}. The SVR rate for genotype 3-infected subjects treated with pegIFN and RBV and with SOF and RBV have been described previously;[13,22] hence, no control group is needed for this open-label exploratory study.

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. Clonal sequencing and population sequencing methods are experimental. EQ-5D-5L and FSS PRO instruments are standards in the literature and thoroughly validated.

5.6.3 Suitability of Subject Population

The selection of subjects infected with HCV genotype 3 virus will allow for the assessment of safety, pharmacokinetics, and antiviral activity of ombitasvir/ABT-450/r and SOF, and if applicable RBV, dosed in combination. Patients chronically (rather than acutely) infected with HCV comprise the target population for DAA-based regimens. This study will enroll subjects who are naïve to treatment and subjects who have previously been treated with pegIFN, RBV, and/or SOF, to assess the impact of prior treatment failure. Previous SOF exposure is not expected to impact the response to SOF in this trial, since SOF exposure does not select persistent resistant variants.

5.6.4 Selection of Doses in the Study

Doses of the DAAs (ombitasvir/ABT-450/r and SOF) to be used in this study have been studied in Phase 3 trials in HCV-infected subjects without cirrhosis and those with compensated cirrhosis. Doses of ABT-450/r and ombitasvir comparable to and higher than the doses to be administered in this study have been studied in single- and multiple-dose healthy volunteer studies and administered to HCV-infected subjects without cirrhosis as monotherapy or in combination with pegIFN/RBV and found to be generally safe and well tolerated. The components of this study regimen and the doses used in this study were administered to more than 2,700 subjects as part of a 3-DAA

treatment regimen. SOF is currently marketed in the US and EU at a dose of 400 mg once daily.

ABT-450/r

The 25/150/100 mg doses of the co-formulated ombitasvir/ABT-450/r tablets will be used in this study. In Study [redacted], ABT-450 200 mg and ritonavir 100 mg dosed with ombitasvir 25 mg and weight-based RBV achieved an SVR rate of [redacted]% in HCV genotype [redacted] infected subjects. However, different formulations of ABT-450 [redacted] ritonavir (soft gelatin capsule) and ombitasvir [redacted] were used in that study. The ombitasvir/ABT-450/r co-formulated tablet dosed at 25/150/100 mg has lower ABT-450 exposures [redacted] compared to the ABT-450 200 mg [redacted] tablet used in Study [redacted].

Since ABT-450 has a [redacted] exposure-response relationship, the [redacted]% decrease in exposure is not expected to impact response.

Based on the [redacted] response rate seen in genotype [redacted]-infected subjects in Study [redacted] higher ABT-450 doses could result in better efficacy. However, because of the [redacted] relationship seen with ABT-450, [redacted] than those achieved in Phase 3 clinical trials for genotype [redacted] infection would be required, and the doses necessary to achieve [redacted] would increase the risk of ALT elevations. Furthermore, when combined with SOF and ombitasvir, 2 agents that are highly active against genotype 3, the 150 mg dose is expected to provide maximal SVR rates.

The maximum dose of ombitasvir/ABT-450/ritonavir 12.5 mg/75 mg/50 mg tablets will not exceed 25 mg/150 mg/100 mg per day for 12 weeks.

Ombitasvir

Based on [redacted] in vitro potencies between HCV genotype [redacted] and HCV genotype [redacted], the same ombitasvir doses were chosen for HCV genotype 3-infected subjects. In vitro activity of ABT-450 against HCV genotype [redacted] is comparable to that against HCV genotype [redacted] using subgenomic replicon cell line.

Ombitasvir exposures from the ombitasvir/ABT-450/r co-formulated tablet are comparable to those from the ombitasvir HME tablet used in Study M12-998. Therefore, the ombitasvir/ABT-450/r co-formulated tablet at the 25/150/100 mg dose is the recommended formulation and dose to be administered with weight-based ribavirin for HCV genotype 3-infected subjects.

The maximum dose of ombitasvir/ABT-450/ritonavir 12.5 mg/75 mg/50 mg tablets will not exceed 25 mg/150 mg/100 mg per day for 12 weeks.

Sofosbuvir

Sofosbuvir is an HCV nucleotide analog NS5B polymerase inhibitor with in vitro activity against genotype 3a,[19] which is approved for use at a dose of 400 mg per day. At this dose, sofosbuvir has been variously studied in genotype 3-infected subjects in combination with RBV, pegIFN, RBV, and the NS5A inhibitor daclatasvir. This dose has been shown to demonstrate significant antiviral activity with minimal treatment limiting toxicities and a safety profile that is similar to that of the AbbVie DAA regimen. Therefore this dose will be used in this study.

The maximum total daily dose of SOF 400 mg tablets administered in this study will not exceed 400 mg per day for 12 weeks.

RBV

In subjects selected to receive RBV-inclusive treatment regimens, the daily dose of RBV in this study is 1000 mg or 1200 mg daily divided BID per local label (e.g., < 75 kg = 1000 mg daily divided BID or ≥ 75 kg = 1200 mg daily divided BID).

This dose is approved for treatment of adult 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 6.7.4. 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, M13-099, and M14-004 and was found to be generally safe and well tolerated, and resulted in high SVR rates in genotype 1 infection.

The maximum RBV dose administered in this study will not exceed 1200 mg, divided twice daily for 12 weeks. RBV dosage will be reduced in subjects with a calculated creatinine clearance < 50 mL/min (Section 6.7.6).

6.0 Adverse Events

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 Definitions

6.1.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [see Section 6.7 regarding toxicity management]) and/or if the investigator considers them to be adverse events.

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

6.1.2 Serious Adverse Events

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

Death of Subject An event that results in the death of a subject.

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

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

6.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug. Assessment of relatedness will be made with respect to the DAAs (ombitasvir/ABT-450/r and SOF) and with respect to RBV:

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

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

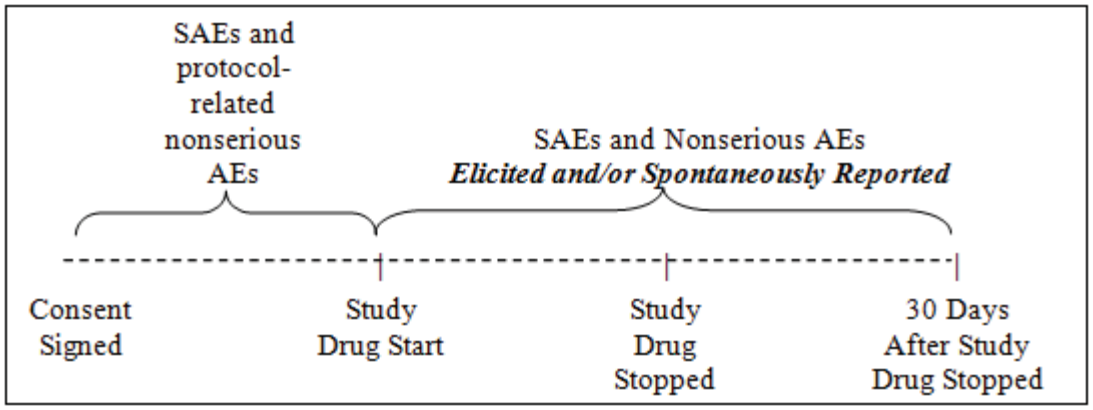
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the SAE.

6.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days following discontinuation of study treatment has elapsed, all adverse events and serious adverse events will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent until 30 days after the last dose of study drug.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.5 Adverse Event Reporting

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

FAX to: [redacted]

Email to:

For safety concerns, contact the Antiviral Safety Team at:

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

[redacted]

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

Primary Study Designated Physician:

[redacted]

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

6.6 Pregnancy

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, starting with Study Day 1 and for 30 days after the end of treatment with DAAs only, or for 7 months after the last dose of RBV (or per local RBV label) and/or consistent with local treatment guidelines for RBV.

Pregnancy in a study subject must be reported to the AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects receiving a RBV-inclusive regimen who report a positive pregnancy test during the Treatment Period must be notified to stop RBV immediately. Administration of DAAs may be continued at the investigator's discretion, if the benefit of continuing therapy is felt to outweigh the risk (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for pregnancies occurring up to 30 days after the end of treatment with DAAs only, or 7 months (or per local RBV label) after the last dose of RBV for treatment with DAAs plus RBV. The investigator is encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry, if RBV is included within the regimen.

Subjects who discontinue study medications due to pregnancy will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

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.

6.7 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. A table of Clinical Toxicity Grades for evaluating laboratory abnormalities is provided in Appendix C. This

table should be used in determination of the appropriate toxicity management as discussed in Section 6.7.1, Section 6.7.2, Section 6.7.3, Section 6.7.4, Section 6.7.5, and Section 6.7.6.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the investigator or AbbVie as having a "reasonable possibility" of being related to the study drug (Section 6.3). A toxicity is deemed "clinically significant" based on the medical judgment of the investigator. Laboratory abnormalities will be managed as deemed clinically appropriate by the investigator until resolved.

Investigators should avoid interrupting study drugs for more than 7 consecutive days. 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.

6.7.1 Grades 1 or 2 Laboratory Abnormalities and Mild or Moderate Adverse Events

Subjects who develop a mild or moderate adverse event or Grade 1 or 2 laboratory abnormality, other than those discussed separately in Section 6.7.4 (Management of Decreases in Hemoglobin), Section 6.7.5 (Management of ALT Elevations), and Section 6.7.6 (Management of Creatinine Clearance), may continue study drugs with follow-up per study protocol and in accordance with local standard of care.

6.7.2 Grades 3 or 4 Laboratory Abnormalities

With the exception of Grade 3 or higher abnormalities of total bilirubin, uric acid, phosphorus, total cholesterol, triglycerides, or glucose (in subjects with a history of diabetes), if a subject experiences a Grade 3 or greater abnormal laboratory parameter during the Treatment Period, the abnormal laboratory test should be repeated. If the Grade 3 or greater abnormality is confirmed, the investigator should assess whether the abnormality can be managed medically 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 serum hemoglobin or in calculated creatinine clearance, or elevations of serum ALT should be managed according to the guidance in Section 6.7.4, Section 6.7.5, and Section 6.7.6 below. Grade 3 or greater abnormalities of total bilirubin, 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.

6.7.3 Severe Adverse Events or Serious Adverse Events

If a subject experiences a severe 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 severe 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.

Severe adverse events and any associated dose interruptions (or discontinuations) should be promptly entered into the appropriate eCRFs.

6.7.4 Management of Decreases in Hemoglobin

For Subjects Not Receiving Ribavirin:

Hemoglobin decreases should be managed according to grade, based on the guidance in Section 6.7.1 and Section 6.7.2 above.

For Subjects Receiving Ribavirin:

Reductions in hemoglobin are a well characterized side effect of ribavirin exposure. If a subject receiving the standard dose of ribavirin experiences a hemoglobin decrease meeting one of the criteria outlined in Table 9, a confirmatory test should be performed. If the hemoglobin decrease is confirmed, the management guidelines in Table 9 should be followed. Management will be different for subjects without a history of known cardiac disease and subjects with known cardiac disease. Subjects experiencing decreases in hemoglobin that do not meet the criteria outlined in Table 9 may need hemoglobin evaluations at more frequent intervals at the discretion of the investigator.

The dose of RBV should not be further modified in subjects with creatinine clearance < 50 mL/min who are receiving a reduced dose of RBV. Reductions in hemoglobin in these subjects should be managed as medically appropriate and as outline in Table 9.

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

Alternate management of hemoglobin decreases outside of these criteria is permitted with approval of the AbbVie Study Designated Physician.

Table 9. Ribavirin Dose Modification Guidelines in Management of Hemoglobin Decreases

Hemoglobin Value	Intervention
Subjects with Creatinine Clearance ≥ 50 mL/min	
< 10 g/L and ≥ 8.5 g/dL	Reduce RBV dose.* Study drugs may be continued. If hemoglobin increases to ≥ 10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose.
< 8.5 g/dL	Interrupt ribavirin. Manage the subject as medically appropriate. If hemoglobin increases to ≥ 8.5 g/dL, RBV may be restarted.
Additional Guidance for Subjects with History of Stable Cardiac Disease and Creatinine Clearance ≥ 50 mL/min	
Hemoglobin decrease of ≥ 2 g/dL during any 4-week treatment period	Reduce RBV dose.* If a subsequent hemoglobin result is greater than the level that triggered the dose reduction, RBV dose may be increased; with gradual dose increases in 200 mg increments.
< 12 g/dL after a 4-week RBV dose reduction	Interrupt ribavirin. Manage the subject as medically appropriate. If subsequent hemoglobin increases to ≥ 12 g/dL, RBV may be restarted.
For Subjects with Creatinine Clearance < 50 mL/min	
< 10 g/L	Interrupt RBV. Manage the subject as medically appropriate. If hemoglobin increases ≥ 10 g/dL, RBV may be restarted. If creatinine clearance increases to ≥ 50 mL/min, refer to guidance above.

* First dose reduction of ribavirin is by 200 mg/day. If needed, second dose reduction of ribavirin is by an additional 200 mg/day. Subjects whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

6.7.5 Management of ALT Elevations

Transient asymptomatic Grade 3 – 4 ALT elevations have been observed in approximately 1% of subjects receiving ABT-450/r-containing regimens. If a subject experiences a post-baseline increase in ALT to > 5 × ULN that is increased from a previous measurement, the subject should have a confirmatory ALT measurement performed.

If the ALT increase is confirmed to be > 5 × ULN and increased from the previous measurement, the recommendations below should be followed:

- Evaluate for alternative etiology of ALT elevation: update medical history and concomitant medications eCRF (if applicable), and obtain additional testing 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.
  - Increasing direct bilirubin, increasing INR, or onset of symptoms/signs of hepatitis.

Alternate management of ALT increases is permitted with approval of the AbbVie Study Designated Physician.

6.7.6 Creatinine Clearance

If calculated creatinine clearance (by Cockcroft-Gault formula) is confirmed to have decreased to < 50 mL/minute (in a subject with a baseline creatinine clearance of ≥ 50 mL/min), or to below 30 mL/min (in a subject with baseline creatinine clearance < 50 mL/min), medical evaluation should include a full review of current medications, including those taken on an as needed basis, those which are sold over the counter and any dietary and herbal supplements, and appropriate dose reduction or discontinuation based on impaired renal function should be done (if applicable). Ribavirin dose should be adjusted as in Table 10. Alternative management of RBV dose in the setting of reduced renal function will require approval of the AbbVie Study Designated Physician.

The investigator should also consider whether drug-drug interactions with concomitant medications may have contributed to the decrease in creatinine clearance, and whether discontinuation or substitution of the possible interacting drug might be considered. For example, drug interactions between DAAs and some antihypertensive medications could potentially increase exposures of the antihypertensive, which may lead to reduction in renal function. If anti-hypertensive medications are adjusted, vital signs should be

monitored to ensure appropriate blood pressure control. Refer to Section 5.2.3 for additional information regarding drug-drug interactions.

Table 10. Dosing of RBV in Subjects with Renal Impairment

CrCl Value	RBV Dose
30 – 50 mL/min	Alternating doses, 200 mg and 400 mg every other day
< 30 mL/min	200 mg daily
Hemodialysis	200 mg daily

Note: For RBV dosing in subjects with concurrent creatinine clearance < 50 mL/min and Hb < 10 (Table 8).

If creatinine clearance improves, the site should perform all necessary readjustments of any dose modifications that have been made. If creatinine clearance improves to above the level that triggered the RBV dose reduction, the RBV dose may be increased accordingly.

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol, except 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 Contacts:

Primary Contact: Alternate Contact:

[redacted]

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

An interim analysis will occur after all enrolled subjects have completed through Post-Treatment Week 12 or prematurely discontinued from the study. The database will be versioned after performing appropriate data cleaning. Final data through Post-Treatment Week 48 will be locked in a later version of the database after appropriate data cleaning is performed.

SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. The intent-to-treat (ITT) population will consist of all enrolled subjects who received at least one dose of study drug. Efficacy, safety, and demographic analyses will be performed on all subjects in the ITT population.

Detailed statistical methods for all endpoints will be provided in the Statistical Analysis Plan (SAP).

No data will be imputed for any efficacy or safety analyses except for analyses of the HCV RNA endpoints.

HCV RNA values will be selected for the SVR_{12} analysis based on defined visit windows. When there is no HCV RNA value in a visit window based on defined visit windows, the closest values before and after the window, regardless of the value chosen for the subsequent and preceding window, will be used for the flanking imputation described below.

If a subject has a missing HCV RNA value at a post-Day 1 visit, but with undetectable or unquantifiable HCV RNA levels at both the preceding value and succeeding value, the HCV RNA level will be considered undetectable or unquantifiable, respectively, at this visit for this subject. For SVR_{12} analysis, if there is no value in the appropriate window but there is an HCV RNA value after the window, then it will be imputed into the SVR_{12} window. Subsequent to this imputation, if a subject is missing a value for the visit window associated with the analysis, the subject will be imputed as a visit failure (i.e., not undetectable or unquantifiable).

8.1.1 Demographics

Demographics and baseline characteristics will be summarized by treatment arm for all subjects in the ITT population. Demographics include age, weight, height, and BMI as continuous variables, and sex, race, age category ([< 55 years or ≥ 55 years] and [< 65 or ≥ 65 years]), and BMI category (< 30 kg/m^2 or ≥ 30 kg/m^2). Baseline characteristics will include: IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), prior treatment history (treatment naïve, pegIFN/RBV null-responder, pegIFN/RBV partial responder, SOF breakthrough/nonresponder, HCV therapy relapser, HCV relapse/breakthrough, HCV therapy nonresponder, pegIFN intolerant, and pegIFN experienced), baseline HCV RNA levels ([continuous] and [< 800,000 IU/mL or ≥ 800,000 IU/mL]), and HCV subgenotype (3, 3a, 3b, or 3c). Summary statistics (N, mean, median, standard deviation [SD], and range) will be generated for continuous variables (e.g., age and BMI). The number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0. The lower limit of detection (LLOD) is 20 IU/mL and results below LLOD are reported as "HCV RNA not detected;" the LLOQ for this assay is 25 IU/mL and results below LLOQ but detectable are reported as" < 25 IU/mL HCV RNA detected."

8.1.2.1 Primary Efficacy Endpoint

The primary endpoint is the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The number and percentage of subjects achieving SVR_{12} will be calculated for each treatment arm and 2-sided 95% Wilson score confidence intervals for a binomial proportion will be computed.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The percentage of subjects in each treatment arm and across all treatment arms with on-treatment virologic failure (rebound defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, or confirmed increase from nadir in HCV RNA at any time point during treatment, or failure to suppress during treatment (all on-treatment values of HCV RNA ≥ LLOQ) with at least 6 weeks (defined as active study drug duration ≥ 36 days) of treatment.
- The percentage of subjects with post-treatment relapse ($relapse_{12}$ defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug (up to and including the SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment. Completion of treatment is defined as study drug duration ≥ 77 days.

The numbers and percentages of the subjects with virologic failure during treatment and with post-treatment relapse will be calculated for each arm. The corresponding 2-sided 95% Wilson score confidence intervals for a binomial proportion will be calculated.

8.1.2.3 Additional Efficacy Endpoints

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

- All reasons for not achieving SVR_{12} for subjects who do not achieve SVR_{12};
- Number and percentage with unquantifiable HCV RNA at each post-baseline visit throughout the Treatment Period (using data from the central laboratory as observed, i.e., no imputation for missing data);
- The percentage of subjects with HCV RNA < LLOQ 24 weeks after the last actual dose of study drug (SVR_{24});
- All reasons for not achieving SVR_{24} for subjects who do not achieve SVR_{24}.
- Time to suppression of HCV RNA (defined as the study day of the first of two successive HCV RNA < LLOQ) during the Treatment Period.

In the above analyses that use the number and percentage of responders, the rates and 2-sided 95% Wilson score confidence interval for a binomial proportion will be calculated. For HCV RNA levels, the time to suppression during treatment will be calculated for each subject, and the median time will be estimated using Kaplan-Meier methodology for right censored observations.

8.1.3 Patient Reported Outcomes

The following exploratory analyses of patient reported outcomes (PROs) will be performed:

- mean change from baseline in EQ-5D-5L health index score and its VAS score to each applicable post-baseline time point
- mean change from baseline in the FSS score and its VAFS score to each applicable post-baseline time point

Summary statistics (n, mean, SD, median, minimum and maximum) at each visit and for change from baseline to each visit will be provided for the EQ-5D-5L health index and its VAS scores, and the FSS and its VAFS scores.

Additional analyses of PROs will be performed as useful and appropriate.

8.1.4 Resistance Analyses

The genes of interest for population sequencing in this study are those encoding full length NS3/4A, NS5A, and NS5B. For clonal sequencing, the DNA encoding NS3 amino acids 1 – 181, NS5A amino acids 1 – 215, and NS5B amino acids 280 – 591 will be sequenced. Amino acid positions where resistance-associated variants have been identified in vitro and/or in vivo in genotype 3 are 56, 80, 155, 156, 166, and 168 in NS3 for ABT-450; 28, 30, 31, 32, 58, and 93 in NS5A for ombitasvir; and 282 in NS5B for sofosbuvir.

Only samples with an HCV RNA level of ≥ 1,000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore if the HCV RNA level at the time of virologic failure or treatment discontinuation is < 1,000 IU/mL, the sample closest in time after the failure/discontinuation with an HCV RNA level ≥ 1,000 IU/mL will be used. Included time points for analyses on samples from subjects who do not achieve SVR_{12} are: 1) time of virologic failure/treatment discontinuation or sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1,000 IU/mL, 2) 24 weeks post-DAA treatment, provided that resistance-associated variants were detected by either population or clonal sequencing at the time of failure/discontinuation, and 3) 48 weeks post-DAA treatment, provided that resistance-associated variants were detected by either population or clonal sequencing at 24 weeks post-DAA treatment. For these samples, clonal sequencing of a given target will be performed only if no variants are detected at signature resistance-associated amino acid positions by population sequencing. In addition, clonal sequencing may be performed if there is a complex mixture of amino acids at a signature resistance-associated position that cannot be resolved by population sequencing.

The following definitions will be used in the resistance analyses:

- Baseline variant: a variant (by population sequencing) in a baseline sample determined by comparison of the amino acid sequence of the baseline sample to the appropriate prototypic reference amino acid sequence for a given DAA target.
- Post-baseline variant by population sequencing: an amino acid variant detected by population sequencing in a post-baseline time point sample that was not detected by population sequencing at baseline in the subject.
- Post-baseline variant by clonal sequencing: a variant at a signature resistance-associated amino acid position that was not present in a subject by population sequencing at baseline, but that is detected in a post-baseline sample from that subject by clonal sequencing in at least 2 clones from that sample (among the subset of subjects for whom clonal sequencing is performed).
- Emerged variant by population sequencing: a post-baseline variant that is observed in samples from 2 or more subjects of the same HCV subgenotype by population sequencing.
- Linked variant by population sequencing: 2 or more signature resistance-associated or emerged amino acid variants identified within a target by population sequencing, and no mixture of amino acids is detected at either position.
- Linked variant by clonal sequencing: at least 2 clones from a given sample containing the same 2 or more signature resistance-associated amino acid variants by clonal sequencing.

Baseline samples will be sequenced by population sequencing for all subjects for whom samples are available. A listing by subject of all baseline variants relative to the appropriate prototypic reference sequence at signature resistance-associated amino acid positions will be provided for each DAA target (NS3, NS5A, and NS5B). In addition, a summary of the number and percentage of subjects with each baseline variant at a signature resistance-associated amino acid position within each target by HCV subgenotype out of the total number of baseline samples sequenced will also be provided.

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

The HCV amino acid sequence as determined by population sequencing on the sample closest in time after virologic failure or treatment discontinuation with an HCV RNA level of ≥ 1,000 IU/mL will be compared to the baseline and appropriate prototypic reference amino acid sequences. Listings by subject of all post-baseline variants detected by population sequencing relative to the baseline amino acid sequences will be provided for each DAA target (NS3, NS5A, and NS5B). Listings by subject of all emerged variants by population sequencing, by amino acid position and variants within a DAA target in a post-baseline sample relative to the baseline amino acid sequence will be provided for each DAA target. In addition, listings by subject of all post-baseline variants (by population sequencing) at signature resistance-associated amino acid positions relative to the appropriate prototypic reference amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B).

The number and percentage of subjects with emerged variants by population sequencing by amino acid position and variant within a DAA target at the time of VF compared to baseline will be summarized. The analyses will be grouped by HCV subgenotype and DAA target (NS3, NS5A, or NS5B).

Linkage between emerged or signature variants by population sequencing will also be evaluated. A listing by subject and time point of the linked variants by population sequencing for each target will be provided.

For the subset of samples for which clonal sequencing is performed, a listing of post-baseline variants by clonal sequencing at signature resistance-associated amino acid positions by subject, amino acid position and variant, as well as time point will be provided for each DAA target. Furthermore, listings of the linked variants by clonal sequencing by subject, DAA target, and time point will be provided.

The persistence of post-baseline variants at signature resistance-associated amino acid positions for each target (NS3, NS5A, and NS5B) will be assessed by population and/or clonal sequencing at Post-Treatment Weeks 24 and 48. Listings by subject and time point of all post-baseline variants relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B). Additionally, the number and percent of subjects in whom an emerged variant persists at Post-Treatment Weeks 24 or 48 out of the total number of subjects with that emerged variant at the failure/discontinuation time point and at Post-Treatment Week 24 and/or Post-Treatment Week 48 will be summarized by HCV subgenotype, DAA target, and variant.

Replicon EC_{50} values may not be obtainable for all samples, but for samples where phenotype data is obtained, the fold change in EC_{50} level at each post-baseline time point where phenotypic analysis was performed will be determined relative to the EC_{50} level of baseline and of prototypic standard.

8.1.5 Safety

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

8.1.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).[24] 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) for each treatment arm and overall. The tabulation of the number of subjects with treatment-emergent adverse events by severity rating and relationship to study drug will also 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 incident for the severity rating table and the most related for the relationship to study drug table. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

Additional analyses will be performed if useful and appropriate.

8.1.5.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized at each visit. The baseline value will be the last measurement prior to the initial dose of study drug. Mean changes from baseline to each Post-Baseline Visit will be summarized descriptively for each treatment arm.

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

In addition, the number and percentage of subjects with post-baseline values meeting pre-specified criteria for Potentially Clinically Significant laboratory values during treatment will be summarized for each arm. Additional analyses will be performed if useful and appropriate.

8.1.5.3 Vital Signs Data

Vital sign measurements will be summarized at each visit during the treatment period. Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each Post-Baseline Visit will be summarized descriptively for each treatment arm. The baseline value will be the last measurement prior to the initial dose of study drugs. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant vital signs values during treatment will be summarized for each treatment arm.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Individual plasma concentrations of ABT-450, ritonavir, ombitasvir, SOF, GS-581007, and RBV will be tabulated and summarized. Individual plasma concentrations of possible

metabolites of ABT-450, ombitasvir, and SOF (other than GS-331007) may be tabulated and summarized if measured and sufficient levels of metabolites are observed.

Values for the pharmacokinetic parameters of ABT-450, ombitasvir, ritonavir, SOF, GS-331007, and RBV including the C_{max}, T_{max}, C_{trough}, and AUC will be summarized and tabulated. 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 a nonlinear mixed-effects modeling (NONMEM) software (Version VI or higher). 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 interest in the analysis. If the estimation of the parameters describing absorption characteristics is not possible then they will be fixed to the values obtained from previous analysis. The evaluation criteria described below will be used to examine the performance of different models.

- Model discrimination will be assessed by a likelihood ratio test comparing objective function values (OFVs) when two competing models are compared. An OFV difference (ΔOFV) of 3.84 will be considered to be significant (χ^2, $p < 0.05$) when two nested models with a difference of one parameter ($df = 1$) are compared. The Akaike's information criterion (AIC) will be used to compare non-nested models.
- Various goodness-of-fit criteria, including diagnostic scatter plots and individual plots of model fits.
- Visual predictive checks or standardized visual predictive checks.
- Plausibility of parameter estimates and precision of parameter estimates.

Covariate-parameter relationships will be tested based on scientific principles or prior knowledge i.e., only 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. Covariate modeling will also be guided by plots of

posterior Bayesian estimates of pharmacokinetic parameters versus covariates (delta plots) or plots of η versus covariates (eta plots). If needed, a generalized additive method (GAM) or another suitable regression/smoothing method may be employed for covariate selection. Several covariate models (linear or nonlinear mathematical functions) will be explored to adequately describe the pharmacokinetic data. A likelihood ratio test will be employed for covariate selection by comparing OFVs obtained from NONMEM. A decrease in the OFV of at least 3.84 (χ^2, $p < 0.05$, $df = 1$) is considered significant in the univariate analysis. A full model will be developed with all significant covariates from the univariate analysis. Finally, backward elimination will be performed to develop a final model. An increase in the OFV of at least 7.88 (χ^2, $p < 0.005$, $df = 1$) will be considered significant in the backward elimination. The AIC will be used to compare non-nested models.

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

The relationship between exposure (e.g., population pharmacokinetic model predicted concentrations over time or average concentrations or AUC or trough concentrations of the individual model-predicted pharmacokinetic profiles, or some other appropriate measure of exposure) and antiviral activity will be explored. Exposure response relationships will be explored using a semi-mechanistic viral dynamic model and/or logistic regression analyses.

The viral dynamic model will account for target cell growth and death, infection of target cells, infected cell infection and death rate, production of virus by infected cells, and inhibition of production of virus by the various DAAs. Effect of RBV will be explored on infection of target cells by virus. Models will explore mutation of the wild type to single and/or double mutant species depending on the available clinical resistance data.

Additional adjustments to the structural and error models will be made during model development as appropriate.

Logistic regression analyses will explore the relationship between exposure and one or more virologic endpoints (e.g., RVR, EVR, SVR_4, SVR_{12}, relapse following end of treatment and breakthrough on treatment).

Additionally, relationships between exposure and safety endpoints of interest may be explored.

8.2 Determination of Sample Size

It is planned to enroll approximately 20 subjects into this study. With a sample size of 10 subjects per arm and an observed SVR_{12} rate of 90%, the 2-sided 95% confidence interval, using Wilson's score confidence interval, will be (59.6%, 98.2%). Subjects who do not have data at PT Week 12 (after performing the described imputation) count as failures for SVR_{12} so no adjustment for dropout is applicable.

From the perspective of safety assessment, the probability that a given adverse event would not be observed among 20 subjects is shown in the second column of Table 11 for various true population incidence rates. With 20 subjects, the probability is at least 97.8% to observe an adverse event with an incidence rate of 10% or higher.

Table 11. Probability of Not Observing an Adverse Event or Lab Abnormality for Various True Incidence Rates

True Incidence Rate	Probability of Not Observing
0.10	0.122
0.20	0.012
0.30	< 0.001
0.40	< 0.001
0.50	< 0.001

8.3 Randomization Methods

Approximately 20 subjects will be randomized to ombitasvir/ABT-450/r 25 mg/150 mg/100 mg QD + sofosbuvir 400 mg QD for 12 weeks (Arm A) or

ombitasvir/ABT-450/r 25 mg/150 mg/100 mg QD + sofosbuvir 400 mg QD + weight-based RBV for 12 weeks (Arm B) in a 1:1 ratio. Randomization will be stratified by IL28B genotype (CC versus non-CC) and prior treatment status (treatment-naïve versus treatment-experienced).

9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, 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.

IL28B genotypes will be determined for each subject. Consent for determination of IL28B status will be included in the study informed consent. Additional pharmacogenetic analysis, other than IL28B analysis and mRNA analysis will only be performed if the subject has voluntarily signed and dated the IEC/IRB approved pharmacogenetic and mRNA informed consents, after the nature of the testing has been explained and the subject has had the opportunity to ask questions. The subject must provide consent specific to pharmacogenetic and mRNA testing before the pharmacogenetic and mRNA testing is performed. If the subject does not consent to the additional pharmacogenetic or mRNA testing it will not impact the subject's participation in the study.

The optional pharmacogenetic analysis will only be performed if the subject has voluntarily signed and dated a separate pharmacogenetic informed consent form, approved by an IRB/IEV, after the nature of the testing has been explained and the subject has had the opportunity to ask questions. The separate pharmacogenetic informed consent

must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's participation in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will

be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

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

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

11.0 Data Quality Assurance

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

12.0 Use of Information

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic 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 pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

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

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

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for ombitasvir and ABT-450, and the product inserts 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:	A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of the Co-Administration of Ombitasvir/ABT-450/Ritonavir (Ombitasvir/ABT-450/r) With Sofosbuvir (SOF) With or Without Ribavirin (RBV) in Subjects With Genotype 3 Chronic Hepatitis C Virus (HCV) Infection
Protocol Date:	31 July 2014

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

1. Weekly Epidemiological Record. No. 41, 7 October 2011, WHO.
2. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2011;34(4 Pt 1):809-16.
3. Sangiovanni A., Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. Hepatology. 2006;43(6):1303-10.
4. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology. 2004;127(5 Suppl 1):S27-34.
5. Serfaty L, Aumaitre H, Chazouilleres O, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology. 1998;27(5):1435-40.
6. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112(2):463-72.
7. Fattovich G, Pantalena M, Zagni I, et al. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. Am J Gastroenterol. 2002;97(11):2886-95.
8. Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Dis. 2000;20(1):1-16.
9. Sy T, Jamal MM. Epidemiology of hepatitis C virus (HCV) infection. Int J Med Sci. 2006;3(2):41-6.
10. Cornberg M, Razavi HA, Alberti A, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int. 2011;31(Suppl 2):30-60.
11. Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol. 2008;48:148-62.
12. Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 4. N Engl J Med. 2008;357:124-34.

13. 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.

14. AbbVie. ABT-450 Investigator Brochure Edition 6. 26 March 2013.

15. AbbVie. ABT-267 Investigator Brochure Edition 4. 26 March 2013.

16. Gilead Sciences. Solvadi US Package Insert. Dec 2013.

17. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368:1878-87.

18. Lawitz E, Sullivan G, Rodriguez-Torres M, et al. A 12-week trial of interferon-free regimens containing ABT-450/r and ABT-267 ± ribavirin in treatment-naïve patients with HCV genotypes 1 – 3. APASL 2013. June 6-10 2013; Suntec City, Singapore.

19. 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;56:3359-68.

20. Eley T, You X, Huang S, et al. Evaluation of drug interaction potential between daclatasvir and sofosbuvir. 8th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 26-27, 2013; Cambridge, MA. Abstract O 14.

21. 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). November 9-13 2012; Boston, MA. Abstract 1888.

22. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002;347:975-82.

23. 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.

24. Medical Dictionary for Regulatory Activities (MedDRA), Version 14.1.

25. Brennan BJ, Wang K, Blotner S, et al. Safety, tolerability, and pharmacokinetics of ribavirin in hepatitis C virus-infected patients with various degrees of renal impairment. Antimicrob Agents Chemother. 2013;57(12):6097-105.

Appendix A. Responsibilities of the Clinical Investigator

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

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

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

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Project Director	CPD
	Sr. Manager	Statistics
	Director	PK
	Sr. Medical Director	CPD
	Clinical Supply Project Manager	GDSM
	CRMA	CPD

Appendix C. Clinical Toxicity Grades

Clinical Toxicity Grades for HCV Studies[1,2]				
	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
HEMATOLOGY				
ABSOLUTE NEUTROPHIL COUNT DECREASED	<LLN – 1500/mm3 <LLN – 1.5 × 10e3/L	<1500 – 1000/mm3 <1.5 – 1.0 × 10e3/L	<1000 – 500/mm3 <1.0 – 0.5 × 10e3/L	<500/mm3 <0.5 × 10e3/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 – 10e3/L	<800 – 500/mm3 <0.8 – 0.5 × 10e3/L	<500 – 200 mm3 <0.5 – 0.2 × 10e3/L	<200/mm3 <0.2 × 10e3/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 × 10e3/L	<3000 – 2000/mm3 <3.0 – 2.0 × 10e3/L	<2000 – 1000/mm3 <2.0 – 1.0 × 10e3/	<1000/mm3 <1.0 × 10e3/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
CALIUM, IONIZED, LOW	<LLN – 1.0 mmol/L	<1.0 – 0.9 mmol/L	<0.9 – 0.8 mmol/L	<0.8 mmol/L
CALCIUM, IONIZED, HIGH	>ULN – 1.5 mmol/L	>1.5 – 1.6 mmol/L	>1.6 – 1.8 mmol/L	>1.8 mmol/L

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

Clinical Toxicity Grades for HCV Studies (Continued)

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

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

Clinical Toxicity Grades for HCV Studies (Continued)

	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
ENZYMES				
ALT/SGPT	>ULN - 3.0 × ULN	>3.0 - 5.0 × ULN;	>5.0 – 20.0 × ULN	>20.0 × ULN
AST/SGOT	>ULN - 3.0 × ULN	>3.0 - 5.0 × ULN;	>5.0 – 20.0 × ULN	>20.0 × ULN
ALKALINE PHOSPHATASE	>ULN – 2.5 × ULN	>2.5 – 5.0 × ULN	>5.0 – 20.0 × ULN	>20.0 × ULN
AMYLASE	>ULN – 1.5 × ULN	>1.5 – 2.0 × ULN	>2.0 – 5.0 × ULN	>5.0 × ULN
LIPASE	>ULN – 1.5 × ULN	>1.5 – 2.0 × ULN	>2.0 – 5.0 × ULN	>5.0 × ULN

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

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

Document Approval

Study M14567 - A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of the Co-Administration of Ombitasvir/ABT-450/Ritonavir (Ombitasvir/ABT-450/r) With Sofosbuvir (SOF) With or Without Ribavirin (RBV) in Subjects With Genotype 3 Chronic Hepatitis C Virus (HCV) Infection - EudraCT 2014-003147-35 - 31Jul2014

Version: 1.0 **Date:** 01-Aug-2014 01:29:59 PM **Abbott ID:** 08012014-00F9F680A1082E-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	31-Jul-2014 07:12:07 PM	Approver
	31-Jul-2014 07:21:15 PM	Approver
	31-Jul-2014 07:24:28 PM	Approver
	31-Jul-2014 10:27:51 PM	Approver
	31-Jul-2014 11:49:16 PM	Approver
	01-Aug-2014 01:29:56 PM	Author