1.0 Title Page

Clinical Study Protocol M14-222

An Open-Label, Multicenter Study to Evaluate Long-term Outcomes with ABT-450/Ritonavir/ ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (TOPAZ II)

Incorporating Amendments 1 and 2, Administrative Change 1, and Amendment 3

AbbVie Investigational Product:	ABT-450/Ritonavir/ABT-267, ABT-333, RBV
Date:	19 December 2014
Development Phase:	3b
Study Design:	Open-label combination drug study
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc.
Sponsor/Emergency Contact:	[redacted] Antiviral Clinical Project Team AbbVie [redacted] 1 North Waukegan Road North Chicago, IL 60064 Phone: Fax: Mobile: [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.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Align the treatment duration for subjects with GT1a infection and compensated cirrhosis (F4 fibrosis stage) with the recommended treatment duration that is found in the US prescribing information for the recently-approved AbbVie product containing the regimen included in this study (i.e., ABT-450/r/ABT-267 and ABT-333). The treatment duration for these patients is extended from 12 to 24 weeks in this amendment, with 12 weeks considered for some patients based on prior treatment history.
- Specify that at least 50, but no more than 110 subjects with fibrosis stage of F3 will be allowed to enroll. Previously, enrollment of these subjects was capped at 100.
- Remove references to a patient portal, which will not be implemented for the study due to administrative reasons.
- Add the contact information for a new Emergency Medical Service that can be contacted by the investigator during a medical emergency if the Primary Study Designated Physician for the study is unavailable.
- Remove the evaluation of adherence to study drug regimens with the Subject Care Plan Model from the secondary objectives. Adherence to the prescribed regimen (measured by pill counts for each type of tablet) will be conducted as a secondary efficacy endpoint.

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-222
Name of Study Drug: ABT-450/r/ABT-267 and ABT-333 with or without Ribavirin (RBV)	**Phase of Development:** 3b
Name of Active Ingredient: ABT-450 Ritonavir ABT-267 ABT-333 Ribavirin	**Date of Protocol Synopsis:** 19 December 2014

Protocol Title:

An Open-Label, Multicenter Study to Evaluate Long-term Outcomes with ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (TOPAZ II)

Primary Objective:

- To evaluate the effect of response to treatment (assessed by SVR_{12} status) on the long-term progression of liver disease in adults with chronic HCV GT1 infection who received treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin, as measured by all-cause death, liver-related death, liver decompensation, liver transplantation, and hepatocellular carcinoma.

Secondary Objectives:

- To evaluate the percentage of subjects achieving a 12-week sustained virologic response, SVR_{12} (HCV RNA < lower limit of quantification [LLOQ] 12 weeks following treatment) in adults with chronic HCV genotype 1 (GT1) infection who receive treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin.
- To assess the change from baseline in quality of life and fatigue following treatment (assessed by Short Form 36 Version 2 health survey [SF-36v2] and the Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT–F]) questionnaires) by baseline fibrosis stage.
- Adherence to the prescribed regimen (measured by pill counts for each type of tablet).

Investigators:

Multi-center trial: Investigator information is on file at AbbVie.

Study Sites:

Approximately 50 US sites.

Study Population:

Adults at least18 years of age, with chronic HCV GT1 infection, with or without compensated cirrhosis, who are treatment-naïve or IFN/RBV (IFN or pegIFN with RBV) treatment-experienced.

Number of Subjects to be Enrolled:

Approximately 600 subjects.

Methodology:

The TOPAZ studies are composed of 2 studies (TOPAZ-I [Study M14-423; to be conducted in non-US regions] and TOPAZ-II [Study M14-222; to be conducted in the US]) due to administrative reasons. This study (TOPAZ-II) is a Phase 3b, open-label, multi-center study designed together with companion study TOPAZ-I, which shares the primary objective of evaluating the effect of SVR_{12} status on the long-term clinical outcomes in adults with GT1 chronic HCV infection with or without compensated cirrhosis, who are either treatment-naïve or IFN/RBV (IFN or pegIFN with RBV) treatment-experienced. In both studies, subjects will be treated with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin (RBV).

Approximately 600 subjects meeting the eligibility criteria will be enrolled at approximately 50 US sites. At least 100, but no more than 150 subjects with fibrosis stage of F4 will be allowed to enroll. At least 50, but no more than 110 subjects with fibrosis stage of F3 will be allowed to enroll. The Metavir score system will be used to interpret the liver biopsy and determine the fibrosis stage. In the absence of a liver biopsy, the equivalent Metavir score corresponding to the results of a screening FibroScan or FibroTest will be used to determine the fibrosis stage.

This study will utilize a Subject Care Plan Model. The subject care plan model is a mechanism that allows subjects to receive reminders for upcoming study visits, reminders to take study drugs, information about their HCV RNA values (if applicable) and/or receive disease specific education and encouragement at varying frequencies of contact.

Subjects will be contacted by a designated nurse educator, contracted by the sponsor, throughout the trial. The nurse educator may interact with subjects by phone, email, in-person visit, postal mail, text message or combinations of these listed communications to facilitate the assigned subject care plan level. After enrollment, the subjects will undergo a subject care plan model assessment that will be conducted by a designated nurse educator. The care plan has three levels as detailed below:

Care Plan Level 1: Subjects that are assessed as requiring a low level of support will be assigned to Care Plan Level 1 and will be contacted approximately 2 to 3 times per week.

Care Plan Level 2: Subjects that are assessed as requiring a moderate level of support will be assigned to Care Plan Level 2 and will be contacted approximately 2 to 3 times per week and receive once daily study medication reminder.

Care Plan Level 3: Subjects that are assessed as requiring a high level of support will be assigned to Care Plan Level 3 and will be contacted approximately 3 to 5 times per week and receive twice daily study medication reminders.

The designated nurse educator will assign a care plan level after their initial assessment and may adjust the care plan level as needed throughout the trial. The subject care plan model support will continue until subjects have completed their Post-Treatment Week 12 Visit.

The study will consist of a Screening Period, Treatment Period and a Post-Treatment Period.

Treatment Period: HCV GT1-infected subjects who are either treatment-naïve or previously treated with IFN/RBV (IFN or pegIFN with RBV) will receive ABT-450/r/ABT-267 and ABT 333. Subjects with HCV GT1a infection and all GT1-infected subjects with compensated cirrhosis will also receive RBV. The treatment duration will be 12 weeks for all subjects except HCV GT1a infected subjects with compensated cirrhosis, who will receive treatment for 24 weeks unless a treatment duration of 12 weeks is selected by the investigator based on the subject's prior treatment history.

Methodology (Continued):

HCV GT1a-infected subjects with compensated cirrhosis who were assigned to 12 weeks of treatment under a previous version of this protocol will be assigned to 12 additional weeks of treatment unless 1) the investigator determines that a 12-week duration of therapy is appropriate based on the subject's prior treatment history; or 2) the subject has already completed the original study drug treatment and additional treatment cannot be initiated within 15 days of the date that the original 12-week treatment was completed.

Post-Treatment Period: Subjects who receive at least one dose of study drug will be followed for up to 260 weeks. All subjects dosed with study drug who complete or prematurely discontinue study drug will be followed in the Post-Treatment Period for 5 years (PT Week 260) and will continue onto their post-treatment care plan (as part of the Subject Care Plan Model) through Post-Treatment Week 12.

The Post-Treatment Period will assess safety, antiviral response, and clinical outcomes, including all-cause death, liver-related death, liver decompensation, occurrence of hepatocellular carcinoma, and liver transplantation.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

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)
   - sexually active with female partners only
   - not of childbearing potential, defined as:
     - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone (FSH) level indicating a postmenopausal state), or
     - surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s);
   - of childbearing potential and sexually active with male partner(s):
     - currently using at least one effective method of birth control at the time of screening and
     - agree 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), starting with Study Day 1 and for 30 days after stopping study drug, or for 6 months after stopping study drug if receiving RBV (Note: Estrogen-containing hormonal contraceptives, including oral, injectable, implantable, patch and ring varieties, may not be used during study drug treatment).
3. Males who are not surgically sterile and 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) throughout the course of the study, starting with starting with Study Day 1 and for 30 days after stopping study drug, or for 6 months after stopping study drug if receiving RBV.

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

Main Inclusion (Continued):

4. Chronic HCV infection prior to study enrollment. Chronic HCV infection is defined as one of the following:
   - Positive for anti-HCV Ab or HCV RNA > 1,000 IU/mL at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
   - HCV RNA > 1,000 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).
5. Screening laboratory result indicating HCV genotype 1-infection.

Main Exclusion:

1. Use of medications listed below, or medications contraindicated for ritonavir or RBV (for those that receive RBV), within 2 weeks or 10 half-lives of the medication whichever is longer, prior to study drug administration including but not limited to:

Alfuzosin	Estrogen-containing Medications for Systemic Use	Phenytoin
Astemizole	Fusidic Acid	Pimozide
Carbamazepine	Gemfibrozil	Rifampin
Dihydroergotamine	Lovastatin	Sildenafil*
Efavirenz	Methylergonovine	Simvastatin
Ergotamine	Midazolam (oral)	St. John's Wort
Ergonovine	Phenobarbital	Terfenadine
		Triazolam

Not all medications contraindicated with 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.

* When used for the treatment of pulmonary arterial hypertension.

2. History of solid organ transplant.
3. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Creatinine clearance (CrCl) < 30 mL/min as estimated by the Cockcroft-Gault equation:
     CrCl = [(140 – Age) × Mass (in kg) × (0.85 if female)] / [72 × Serum creatinine (in mg/dL)]
   - Albumin < 2.8 g/dL
   - Hemoglobin < LLN
   - Platelets < 25,000 cells per mm^3
   - Total bilirubin > 3.0 mg/dL
4. Any current or past clinical evidence of Child-Pugh B or C Classification (Child-Pugh Score ≥ 7) or clinical history of liver decompensation such as ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.
5. Confirmed presence of hepatocellular carcinoma indicated on imaging techniques such as computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or on an ultrasound performed at Screening (a positive ultrasound result will be confirmed with CT scan or MRI).

Investigational Products:	ABT-450/ritonavir/ABT-267 75 mg/50 mg/12.5 mg tablet ABT-333 250 mg tablet Ribavirin 200 mg tablet
Doses:	ABT-450/ritonavir/ABT-267 150/100/25 mg QD ABT-333 250 mg BID Ribavirin weight-based dosing 1000 or 1200 mg divided twice daily
Mode of Administration:	Oral
Reference Therapy:	N/A
Dose:	N/A
Mode of Administration:	N/A

Duration of Treatment:

Subjects will receive ABT-450/r/ABT-267 and ABT-333 with or without RBV for 12 or 24 weeks.

Criteria for Evaluation:

Efficacy:

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

Clinical outcomes related to death and the liver will be assessed during treatment and post-treatment.

Patient Reported Outcomes (PROs):

During treatment and post-treatment, fatigue and general health related quality of life will be assessed using Short Form 36 Version 2 (SF-36v2) health survey and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT–F) questionnaires.

Safety:

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

Statistical Methods:

Efficacy:

The primary efficacy endpoint is the effect of response to treatment on clinical outcomes, based on subjects in this study and companion study TOPAZ-I. The endpoint will be assessed by comparing the incidence of the following events between subjects who achieve SVR_{12} and those who do not, using the Cox regression model:

- All-cause death
- Liver-related death
- Liver decompensation
- Liver transplantation
- Hepatocellular carcinoma
- Composite of any of the above outcomes

Statistical Methods (Continued):

Efficacy (Continued):

The secondary efficacy endpoints are:

1) The percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The SVR_{12} rate and corresponding 2-sided 95% confidence interval using the Wilson score method for the binomial proportion will be presented.

2) The mean change from baseline in quality of life and fatigue to Post-Treatment Week 12 and to Post-Treatment Week 24 (assessed by Short-Form 36 Version 2 health survey (SF-36v2) and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT–F) questionnaires) will be assessed by subjects' fibrosis stage at baseline using an ANCOVA model with baseline fibrosis stage as the factor and baseline PRO score and SVR_{12} status as covariates.

3) Adherence to the prescribed regimen (measured by pill counts for each type of tablet).

Safety:

The overall 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. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by severity rating and relationship to study drug. Change from baseline in laboratory tests and vital sign measurements to each time point of collection will be summarized. 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 will be calculated.

Resistance:

The following resistance information will be provided for a subset of the subjects who experience virologic failure: 1) the amino acid variants at baseline at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the appropriate prototypic reference 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 baseline sequence, and 3) 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.

In addition, the persistence of viral resistance-associated amino acid variants will be evaluated in selected samples during the 5-year (through PT Week 260) Post-Treatment Period.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ABT-450/r	ABT-450 administered with ritonavir
ABT-450/r/ABT-267	ABT-450 co-formulated with ritonavir and ABT-267
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	Twice Daily
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CrCl	Creatinine clearance
CRF	Case report form
CYP3A	Cytochrome P450 3A
DAA	Direct-acting antiviral agent
DDI	Drug-Drug interactions
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
FACIT–F	The Functional Assessment of Chronic Illness Therapy – Fatigue
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody

HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
IL28B	Interleukin 28B
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
IU	International units
IUD	Intrauterine Device
LCB	Lower confidence bound
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
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
PCR	Polymerase chain reaction
PegIFN	Pegylated-interferon alfa-2a or 2b
POR	Proof of Receipt
PRO	Patient Reported Outcomes
PT	Post-Treatment
QD	Once daily
r	Ritonavir
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase PCR
SAE	Serious adverse event

SAS	Statistical Analysis System
SF-36v2	Short-Form 36 Version 2 health survey
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR_{12}	Sustained virologic response 12 weeks post- treatment
ULN	Upper limit of normal
USPI	United States Proscribing Information
WBC	White blood cells

Definition of Terms

Study Drug	ABT-450/ritonavir/ABT-267, ABT-333, ribavirin
Day 1	First day a subject took study drug
Treatment Period	Baseline/Day 1 through the last dose of study drug
Post-Treatment Period	Day after the last dose of study drug through Post-Treatment Week 260 or Post-Treatment Discontinuation

2.0 Table of Contents

1.0 Title Page 1
1.1 Protocol Amendment: Summary of Changes 2
1.2 Synopsis 3
1.3 List of Abbreviations and Definition of Terms 9
2.0 Table of Contents 12
3.0 Introduction 17
3.1 Differences Statement 26
3.2 Benefits and Risks 27
4.0 Study Objectives 29
5.0 Investigational Plan 29
5.1 Overall Study Design and Plan: Description 29
5.1.1 Screening 34
5.1.1.1 Rescreening 34
5.1.2 Treatment Period (TP) 34
5.1.3 Post-Treatment (PT) Period 36
5.2 Selection of Study Population 37
5.2.1 Inclusion Criteria 38
5.2.2 Exclusion Criteria 39
5.2.3 Prior, Concomitant, and Prohibited Therapy 42
5.2.3.1 Prior Therapy 42
5.2.3.2 Concomitant Therapy 42
5.2.3.3 Prohibited Therapy 44
5.3 Efficacy and Safety Assessments/Variables 44
5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart 44
5.3.1.1 Study Procedures 49
5.3.1.2 Blood Samples for Pharmacogenetic Analysis 62
5.3.1.3 Meals and Dietary Requirement 62
5.3.2 Efficacy Variables 63
5.3.2.1 Primary Variable 63
5.3.2.2 Secondary Variables 63
5.3.3 Safety Variables 63

5.3.4 Pharmacogenetic Variable 63
5.4 Removal of Subjects from Therapy or Assessment 64
5.4.1 Discontinuation of Individual Subjects 64
5.4.2 Discontinuation of Entire Study 65
5.4.3 Discontinuation of Subjects Meeting Virologic Failure Criteria 65
5.5 Treatments 66
5.5.1 Treatments Administered 66
5.5.2 Identity of Investigational Products 67
5.5.2.1 Packaging and Labeling 67
5.5.2.2 Storage and Disposition of Study Drugs 68
5.5.3 Method of Assigning Subjects to Treatment Groups 68
5.5.4 Selection and Timing of Dose for Each Subject 69
5.5.5 Blinding 69
5.5.6 Treatment Compliance 69
5.5.7 Drug Accountability 70
5.6 Discussion and Justification of Study Design 71
5.6.1 Discussion of Study Design and Choice of Control Groups 71
5.6.2 Appropriateness of Measurements 71
5.6.3 Suitability of Subject Population 72
5.6.4 Selection of Doses in the Study 72
6.0 Adverse Events 73
6.1 Definitions 73
6.1.1 Adverse Event 73
6.1.2 Serious Adverse Events 75
6.2 Adverse Event Severity 76
6.3 Relationship to Study Drug 76
6.4 Adverse Event Collection Period 77
6.5 Adverse Event Reporting 78
6.6 Pregnancy 79
6.7 Toxicity Management 80
6.7.1 Grade 1 or 2 Laboratory Abnormalities and Mild or Moderate Adverse Events 81
6.7.2 Grade 3 or 4 Laboratory Abnormalities 81

6.7.3 Severe Adverse Events or Serious Adverse Events 82
6.7.4 Management of Decreases in Hemoglobin 82
6.7.5 Management of ALT Elevations 84
6.7.6 Creatinine Clearance 85
7.0 Protocol Deviations 86
8.0 Statistical Methods and Determination of Sample Size 87
8.1 Statistical and Analytical Plans 87
8.1.1 Demographics 89
8.1.2 Efficacy 89
8.1.2.1 Primary Efficacy Endpoint 90
8.1.2.2 Secondary Efficacy Endpoints 90
8.1.2.3 Subgroup Analyses 91
8.1.2.4 Additional Efficacy Endpoints 91
8.1.3 Resistance 92
8.1.4 Safety 93
8.1.4.1 Adverse Events 94
8.1.4.2 Clinical Laboratory Data 94
8.1.4.3 Vital Signs Data 95
8.2 Determination of Sample Size 95
8.3 Randomization Methods 95
9.0 Ethics 95
9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB) 95
9.2 Ethical Conduct of the Study 96
9.3 Subject Information and Consent 96
10.0 Source Documents and Case Report Form Completion 97
10.1 Source Documents 97
10.2 Case Report Forms 97
11.0 Data Quality Assurance 99
12.0 Completion of the Study 99
13.0 Investigator's Agreement 100

14.0 Reference List 101

List of Tables

Table 1. Pooled SVR_{12} Rates (Intent-to-treat, missing = failure) from Phase 3 Studies by Subpopulation of Subtype, Prior Treatment History, and Presence or Absence of Cirrhosis 19
Table 2. Overview of Treatment-Emergent Adverse Events (AE) 23
Table 3. Treatment-Emergent Adverse Events with ≥ 10% Frequency in at Least One Arm of the Analysis and Rates of Key Post-Baseline Lab Abnormalities 24
Table 4. Baseline Fibrosis Stage 32
Table 5. Study Drug Regimen 35
Table 6. Medications Contraindicated for Use with the Study Drug Regimen 40
Table 7. Study Activities 45
Table 8. Clinical Laboratory Tests 52
Table 9. Child-Pugh Classification of Severity of Cirrhosis 56
Table 10. Identity of Investigational Products 67
Table 11. Study Drug Storage Conditions 68
Table 12. Ribavirin Dose Modification Guidelines in Management of Hemoglobin Decreases 84
Table 13. Dosing of RBV in Subjects with Renal Impairment 86

List of Figures

Figure 1. Study Schematic 32
Figure 2. Adverse Event Collection 78

List of Appendices

Appendix A. Responsibilities of the Clinical Investigator 105
Appendix B. List of Protocol Signatories..... 107
Appendix C. Clinical Toxicity Grades 108
Appendix D. Protocol Amendment : List of Changes 111

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] Because a majority of patients are believed to have acquired their infection as young adults in the 1970s,[9,10] the number of patients chronically infected for more than 20 years continues to rise,[11,12] and the prevalence of cirrhosis and related complications is expected to increase.[13] In a cohort study of patients with HCV from the United States Department of Veterans Affairs (VA), the prevalence of cirrhosis has increased significantly over the past 10 years.[14] Based on a multicohort natural history model, the proportion of patients with cirrhosis in the United States is projected to reach 25% in 2010 and 45% in 2030.[15]

Treatment of HCV-infected patients could reduce the risk of cirrhosis, decompensation, cancer and liver-related deaths. Among patients from the VA treated with pegylated interferon (pegIFN) and ribavirin therapy, achieving a sustained virologic response (SVR) was associated with significant reduction in all-cause death compared to subjects who did not achieve SVR (5-year mortality rate in HCV genotype 1-infected patients: 6.7% versus 14.4%, respectively).[16] In addition, the 5-year occurrence of the composite clinical events of death, liver failure, and hepatocellular carcinoma were significantly lower in HCV-infected patients with advanced fibrosis or cirrhosis who achieved SVR versus those without SVR (9.2% versus 28.2%, respectively).[17] Patients with SVR following treatment with pegIFN with or without ribavirin (RBV) have also shown improvement in liver histology and a reduction in liver-related mortality in several studies.[18-20] Moreover, , patients with compensated cirrhosis who achieve SVR essentially eliminate their

subsequent risk of decompensation, may achieve histologic regression, and decrease their risk of hepatocellular carcinoma by two-thirds.[21-23] In patients with advanced fibrosis and d cirrhosis, viral suppression by more than 4 $\log_{10}$ with pegIFN and RBV was associated with marked reduction in death/liver transplantation, and in liver-related morbidity and mortality.[24]

Combinations of direct-acting antiviral agents (DAAs) targeting different steps of viral replication have the potential to significantly improve HCV treatment compared to the current interferon-containing regimens for HCV genotype 1 infection by increasing SVR rates, eliminating IFN as a component of therapy, increasing the safety and tolerability of treatment, shortening duration of therapy and simplifying the treatment algorithm. In addition, wider application of DAA therapy and better responses with combination DAA regimens could significantly reduce the public health burden of this disease.

AbbVie's IFN-free regimen for the treatment of chronic HCV genotype 1 infection includes 3 DAAs targeting different steps in HCV replication. ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor co-administered with the pharmacokinetic enhancer, ritonavir (ABT-450/r); ABT-267 (ombitasvir) is a NS5A inhibitor, and ABT-333 (dasabuvir) is a NS5B non-nucleoside polymerase inhibitor. The 3-DAA regimen has been studied with and without ribavirin in over 2,300 patients in Phase 3 trials across a variety of patient populations including those with compensated cirrhosis. Based on Phase 3 data, the regimen with or without RBV appears to be safe, well tolerated and efficacious in treatment-naïve and treatment-experienced HCV genotype 1-infected subjects including those with compensated cirrhosis. The overall efficacy results (intent to-treat) from the Phase 3 studies are listed in Table 1.[31-35]

Table 1. Pooled SVR_{12} Rates (Intent-to-treat, missing = failure) from Phase 3 Studies by Subpopulation of Subtype, Prior Treatment History, and Presence or Absence of Cirrhosis

Subpopulation	3-DAA 12 Weeks SVR_{12}	3-DAA + RBV 12 Weeks SVR_{12}	3-DAA + RBV 24 Weeks SVR_{12}
Genotype 1b non-cirrhotic			
Naïve	99.0	98.9	--
Null	100	94.4	--
Partial	100	98.1	--
Relapser	100	98.5	--
Genotype 1a non-cirrhotic			
Naïve	90.2	95.7	--
Null	--	95.4	--
Partial	--	100	--
Relapser	--	94.0	--
Genotype 1b cirrhotic			
Naïve	--	100	100
Null	--	100	100
Partial	--	85.7*	100
Relapser	--	100	100
Genotype 1a cirrhotic			
Naïve	--	92.4	92.9
Null	--	80.0	92.9
Partial	--	100	100
Relapser	--	93.3	100

* Based on N = 7; 6/7 achieved SVR.

Phase 3 Placebo-Controlled Studies: Studies M11-646 and M13-098

Study M11-646 and Study M13-098 are randomized, placebo-controlled studies that assessed the safety and efficacy of 12 weeks of therapy with 3 DAA + RBV in HCV genotype 1-infected treatment-naïve subjects (Study M11-646) and prior pegIFN/RBV non-responders (Study M13-098) without cirrhosis. Subjects received 3-DAA + RBV for 12 weeks of treatment. Subjects randomized to the placebo arm received placebo for 12 weeks, after which they received open-label 3-DAA + RBV for 12 weeks.

In Study M11-646, a total of 631 subjects were randomized and received at least one dose of study drug, of which 67.7% had HCV genotype 1a and 32.3% had HCV genotype 1b. The SVR_{12} rate for treatment-naïve subjects receiving 3-DAA + RBV for 12 weeks was 96.2%. Virologic failure was noted in 7/322 (2.2%) genotype 1a subjects (on treatment virologic failure: n = 1; relapse: n = 6) and 1/151 (0.7%) genotype 1b subjects (relapse).

In Study M13-098, a total of 394 subjects were randomized and received at least one dose of study drug, of which 58.4% had HCV genotype 1a, 41.4% had HCV genotype 1b, 49.0% were prior pegIFN/RBV null responders, 21.9/% were prior pegIFN/RBV partial responders, and 29.2% were prior pegIFN/RBV relapsers. The SVR_{12} rate for treatment-experienced subjects receiving 3-DAA + RBV for 12 weeks was 96.3%. Virologic failure (all relapse) was noted in 5/173 (2.9%) genotype 1a subjects and 2/123 (1.6%) genotype 1b subjects.

Phase 3 Regimen-Controlled Studies: Studies M13-389, M13-961 and M14-002

Studies M13-389, M13-961, and M14-002 are randomized, regimen-controlled trials that assessed the safety and efficacy of 12 weeks of treatment with 3 DAAs with or without RBV. Study M13-961 and Study M14-002 are placebo-controlled studies, while Study M13-389 is an open-label study. The patient population was different in each of the 3 studies. Study M13-389 enrolled genotype 1b-infected subjects with prior non-response to pegIFN/RBV, M13-961 enrolled genotype 1b-infected subjects who were treatment-naïve, and Study M14-002 enrolled genotype 1a-infected subjects who were treatment-naïve. All three studies excluded subjects with cirrhosis.

In Study M13-389, a total of 186 subjects were randomized and received at least one dose of study drug, of which 34.9% were prior pegIFN/RBV null responders, 28.5% were prior pegIFN/RBV partial responders, and 36.6% were prior pegIFN/RBV relapsers. The SVR_{12} rates were 96.6% in the 3-DAA + RBV arm and 100% in the 3-DAA without RBV arm. The difference in SVR_{12} rates between the 2 regimens met the protocol-specified criteria for noninferiority; hence, the 3-DAA regimen without RBV demonstrated

noninferiority compared to 3-DAA + RBV. No subject in either arm experienced on-treatment virologic failure or post-treatment relapse.

In Study M13-961, a total of 419 subjects were randomized and received at least one dose of study drug. The SVR_{12} rates for treatment-naïve subjects with HCV genotype 1b infection who received either 3 DAAs with or without RBV for 12 weeks were 99.5% and 99.0%, respectively. The difference in SVR_{12} rates between the 2 regimens in this study also met the protocol-specified criteria for noninferiority. One of the 419 treated subjects (3-DAA + RBV arm) experienced on-treatment virologic failure.

In Study M14-002, 305 subjects were randomized and received at least one dose of study drug. The SVR_{12} rates for treatment-naïve subjects with HCV genotype 1a infection who received either 3 DAAs with or without RBV for 12 weeks in Study M14-002 were 97.0% and 90.2%, respectively. The SVR_{12} rate in the 3-DAA arm did not achieve noninferiority to the 3-DAA + RBV arm. Virologic failure was noted in 2/100 (2.0%) subjects (on treatment virologic failure: n = 1; relapse: n = 1) in the RBV-containing regimen and 16/205 (7.8%) subjects (on treatment virologic failure: n = 6; relapse: n = 10) in the RBV-free regimen. The difference between arms demonstrates that RBV contributes to the efficacy in genotype 1a-infected patients and suggests that 3-DAA + RBV is the optimal regimen for these patients.

Phase 3 Study in Cirrhotics: Study M13-099

Study M13-099 is a randomized, multicenter, open-label trial in treatment-naïve subjects or subjects previously treated with pegIFN/RBV with chronic HCV genotype 1 infection with compensated (Child-Pugh A, score ≤ 6) cirrhosis. The 3 DAAs + RBV were administered for either 12 or 24 weeks of treatment.

A total of 380 subjects were randomized and received at least one dose of study drug, of which 68.7% had HCV genotype 1a, 31.3% had HCV genotype 1b, 42.1% were treatment-naïve, 36.1% were prior pegIFN/RBV null responders, 8.2% were prior pegIFN/RBV partial responders, and 13.7% were prior pegIFN/RBV relapsers.

The SVR_{12} rates for subjects with compensated cirrhosis treated with 3-DAA + RBV for 12 or 24 weeks were 91.8% and 95.9%, respectively. Virologic failure was noted in 13/208 (6.3%) subjects (on treatment virologic failure: n = 1; relapse: n = 12) receiving the 12-week regimen and 4/172 (2.3%) subjects (on treatment virologic failure: n = 3; relapse: n = 1) receiving the 24-week regimen.

Analyses of subgroups suggest that the overall difference in SVR_{12} rates was driven largely by a lower SVR_{12} rate among genotype 1a prior null responders who received 12 weeks of treatment, while other subgroups had comparable response rates when treated for 12 or 24 weeks. Thus, a 12-week treatment regimen is recommended for all patients with cirrhosis with the exception of genotype 1a prior null responders, for whom 24 weeks of treatment provides a higher SVR.

Integrated Safety Results

A summary of treatment-emergent adverse events from the pooled analyses of data from the phase 3 studies is presented in Table 2. 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 2. 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

PBO = Placebo

a. Lung cancer.

The most common adverse events regardless of causality are listed in Table 3.

Adverse events that occurred at a ≥ 5% incidence in the 3-DAA + RBV regimen versus the 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 3. 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	
	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
Treatment-Emergent Adverse Events, %	**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

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 may occur due to ABT-450 inhibition of the bilirubin transporters OATP1B1 and OATP1B3, and RBV-induced hemolysis. The elevations generally peaked by Weeks 1 – 2, declined through the end of treatment and returned to within the normal range by 4 weeks post-treatment. Rates of

hyperbilirubinemia were lower in subjects treated with 3-DAA without RBV compared to 3-DAA with RBV. The rates and degree of hyperbilirubinemia were higher in patients with cirrhosis, but the temporal pattern of elevation followed by resolution was similar and few were symptomatic (jaundice). Rates of ≥ grade 2 hemoglobin reductions were 6% among subjects without cirrhosis who received the 3-DAA + RBV regimen for 12 weeks, and 7% and 11% among 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; use of hematologic growth factors and blood transfusion were rare. The anemia reported in the clinical trials was primarily observed when the 3-DAA regimen was administered with 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 hepatic panel. 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 greater than 5 times 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, ABT-267 (and its major, inactive human metabolites) and ABT-333 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

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

In summary, the 3-DAA regimen, with or without RBV, was well tolerated with a low discontinuation rate. Adverse events were typically mild, and many of the adverse events and laboratory abnormalities observed were attributable to the presence of RBV. Transient, asymptomatic serum ALT elevations were observed at a low rate, were not associated with hepatic dysfunction and generally resolved with ongoing treatment.

A detailed discussion of the preclinical toxicology, metabolism, pharmacokinetics and drug-drug interactions can be found in the Investigator's Brochure for ABT-267, ABT-450, ABT-333 and product label for ritonavir and ribavirin.[25-29]

The current study is intended to evaluate the long-term outcomes with ABT-450/r/ABT-267 and ABT-333 with or without RBV for treatment-naïve and IFN/RBV treatment-experienced adults with chronic HCV GT1 infection, with or without compensated cirrhosis.

3.1 Differences Statement

The combination of 3-DAA with or without RBV for 12 and 24 weeks was explored in treatment-naïve and pegIFN/RBV treatment-experienced HCV GT1-infected subjects, with (12 and 24 weeks) or without (12 weeks only) compensated cirrhosis, in several phase 3 studies, These Phase 3 studies have been conducted in a randomized, controlled, double-blind or open-label fashion. This study is a Phase 3b, single arm, open-label study in approximately 600 treatment-naïve and IFN/RBV treatment-experienced subjects with or without compensated cirrhosis.

This is the first study to evaluate SVR_{12} and clinical outcomes through 5 years following treatment with 3-DAA with or without RBV for 12 or 24 weeks in chronic HCV GT1-infected subjects. The study population comprises HCV GT1a- and 1b-infected subjects in the United States who are treatment- naïve or IFN/RBV treatment-experienced. The study will include up to 25% of subjects with compensated

cirrhosis which approximates the projected prevalence among chronic HCV-infected subjects in the United States.[15]

3.2 Benefits and Risks

This Phase 3b study is a single arm study in which eligible HCV genotype 1-infected subjects will receive ABT-450/r/ABT-267 and ABT-333 with or without RBV for either 12 or 24 weeks. The combination of 3-DAA with or without RBV has been evaluated in several phase 3 studies. Treatment with 3-DAA + RBV for 12 weeks resulted in SVR_{12} in 96.2% of HCV GT1-infected, treatment-naïve subjects without cirrhosis in Study M11-646, and in 96.3% of HCV GT1-infected, pegIFN/RBV treatment-experienced subjects without cirrhosis in Study M13-098. In Study M13-961, 99.5% and 99.0% of HCV GT1b-infected treatment-naïve subjects without cirrhosis achieved SVR_{12} following treatment with 3-DAA with or without RBV for 12 weeks, respectively. Similarly, in Study M13-389, 96.6% and 100% of HCV GT1b-infected pegIFN/RBV treatment-experienced subjects without cirrhosis achieved SVR_{12} following treatment with 3-DAA, with or without RBV for 12 weeks, respectively. ABT-450/r/ABT-267 and ABT-333 with or without RBV was also evaluated in Study M14-002. In Study M14-002, 97.0% and 90.2% of HCV GT1a-infected treatment-naïve subjects achieved SVR_{12} following treatment with and without RBV, respectively, suggesting that 3-DAA with RBV is the optimal regimen for HCV GT1a-infected subjects. In this study, HCV GT1a infected subjects will receive 3-DAA with RBV.

The likelihood of successfully curing HCV in compensated cirrhotic subjects following treatment with ABT-450/r/ABT-267 and ABT-333 coadministered with RBV was evaluated in Study M13-099. In Study M13-099, 91.8% and 95.9% of HCV GT1-infected treatment-naïve and pegIFN/RBV treatment-experienced subjects achieved SVR_{12} following treatment for 12 and 24 weeks, respectively. Analysis of subgroups demonstrated that the difference in SVR_{12} rates between treatment arms was due to the lower SVR_{12} rate in GT1a-infected pegIFN/RBV treatment-experienced prior null responders treated for 12 weeks. Among HCV GT1a-infected subjects, partial responders

and relapsers had higher SVR rates than null responders in the 12-week treatment group, while similar SVR rates were seen among the null responders, partial responders and relapsers treated for 24 weeks. SVR rates were high across all subgroups in HCV GT1b-infected subjects treated for 12 and 24 weeks. For this reason, in previous versions of the protocol, HCV GT1a-infected subjects with compensated cirrhosis and who were prior null responders to IFN/RBV were assigned to receive 3-DAA with RBV for 24 weeks, while HCV GT1a-infected subjects with compensated cirrhosis who were not prior null responders to IFN/RBV were assigned to received 3-DAA with RBV for 12 weeks. In order to align the treatment duration for subjects with GT1a infection and compensated cirrhosis with the recommended treatment duration that is found in the US prescribing information for the recently-approved AbbVie product containing the regimen included in this study (i.e., ABT-450/r/ABT-267 and ABT-333), the protocol now specifies that all HCV GT1a-infected subjects with compensated cirrhosis will be assigned to receive 3-DAA with RBV for 24 weeks, unless a treatment duration of 12 weeks is selected by the investigator based on the subject's prior treatment history. HCV GT1a-infected subjects with compensated cirrhosis who were assigned to 12 weeks of treatment under a previous version of this protocol will be assigned to 12 additional weeks of treatment unless 1) the investigator determines that a 12-week duration of therapy is appropriate based on the subject's prior treatment history; or 2) the subject has already completed the original study drug treatment and additional treatment cannot be initiated within 15 days of the date that the original treatment was completed.

ABT-450/r, ABT-267 and ABT-333 with or without RBV have been well tolerated in the Phase 3 studies. Adverse events that are known, and those not previously described, may occur with the DAAs or RBV as detailed in the informed consent for this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures.

Risks associated with ABT-450/r/ABT-267 and ABT-333 coadministered with or without RBV, including the risks of toxicity and virologic failure, appear limited and manageable

based on the results from the phase 3 studies. Given the potential high rate of cure in HCV GT1-infected subjects, the risk-benefit profile is favorable.

4.0 Study Objectives

Primary Objective(s):

- To evaluate the effect of response to treatment (assessed by SVR_{12} status) on the long-term progression of liver disease in adults with chronic HCV GT1 infection who received treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin, as measured by all-cause death, liver-related death, liver decompensation, liver transplantation, and hepatocellular carcinoma.

Secondary Objectives:

- To evaluate the percentage of subjects achieving a 12-week sustained virologic response, SVR_{12} (HCV RNA < lower limit of quantification [LLOQ] 12 weeks following treatment) in adults with chronic HCV genotype 1 (GT1) infection who receive treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin.
- To assess the change from baseline in quality of life and fatigue following treatment (assessed by Short-Form 36 Version 2 health survey (SF-36v2) and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT–F) questionnaires) by baseline fibrosis stage.
- Adherence to the prescribed regimen (measured by pill counts for each type of tablet).

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3b, open-label, multi-center study designed together with companion study TOPAZ-I, which shares the primary objective of assessing the effect of treatment response on long-term clinical outcomes in adults with GT-1 chronic HCV infection with

or without compensated cirrhosis, who are either treatment-naïve or IFN/RBV (IFN or peg IFN/RBV) treatment-experienced. In both studies, subjects will be treated with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin (RBV).

In the TOPAZ-I and TOPAZ-II studies, the primary objective is to assess the effect of treatment response (SVR_{12}) on long-term clinical outcomes, based on the data from both studies combined. The studies differ based on geographic region (this study will be conducted in the US while the TOPAZ-I study will be conducted outside the US) and based on certain procedures that are not related to the primary outcome. For example, this study will utilize a Subject Care Plan Model to facilitate subjects' adherence to the study drugs, and the TOPAZ-I study will assess the long-term change from baseline in liver elastography.

Subjects will be considered to be non-cirrhotic based on a liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis (e.g., a METAVIR Score of 3 or less, Ishak score of 4 or less) or, if a liver biopsy is unavailable, a screening FibroScan® result of < 12.5 kPa or a screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2.

Subjects will be considered to have cirrhosis based on previous histologic diagnosis of cirrhosis on a liver biopsy (e.g., Metavir Score of > 3 [including 3 – 4 or 3/4], Ishak score of > 4) or, if a liver biopsy is unavailable, a screening FibroScan score ≥ 14.6 kPa or a screening FibroTest > 0.72 and APRI > 2.

In the absence of a qualifying liver biopsy, subjects with a screening FibroScan result that is ≥ 12.5 kPa and < 14.6 kPa, a FibroTest result that is ≤ 0.72 and an APRI > 2, or a FibroTest result that is ≥ 0.73 and an APRI ≤ 2, should be evaluated based on the investigator's clinical judgment to determine the presence or absence of cirrhosis.

Subjects will be considered treatment-naïve if they have never received any antiviral treatment for hepatitis C infection.

Subjects will be considered treatment-experienced if they have received prior IFN/RBV (IFN or pegIFN with RBV) excluding DAAs. Subjects with HCV RNA levels that document the type of prior response to IFN/RBV treatment will be categorized as one of the following:

- 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 IFN/RBV or pegIFN/RBV treatment course;
- Partial responder: achieved at least a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior IFN/RBV or pegIFN/RBV treatment course but failed to achieve HCV RNA undetectable at the end of treatment;
- Relapser: achieved HCV RNA undetectable at end of a prior IFN/RBV or pegIFN/RBV treatment course but HCV RNA was detectable following cessation of therapy.

Subjects with a less well-characterized IFN/RBV treatment experience, including those subjects with incomplete HCV RNA and treatment date documentation, will be categorized as one of the following:

- Prior relapse/breakthrough: Achieved at least one documented result of HCV RNA undetectable during a prior IFN/RBV or pegIFN/RBV treatment course.
- Prior nonresponder: Did not achieve a documented result of HCV RNA undetectable or HCV RNA was detected at the end of treatment during a prior IFN/RBV or pegIFN/RBV treatment course, with insufficient data available to categorize as a breakthrough, partial or null responder.
- IFN intolerant: Did not meet any of the above definitions of treatment-failure and discontinued IFN/RBV or pegIFN/RBV therapy due to IFN or pegIFN intolerability.

The study is designed to enroll approximately 600 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.

At least 100, but no more than 150 subjects with fibrosis stage of F4 will be allowed to enroll. At least 50, but no more than 110 subjects with fibrosis stage of F3 will be allowed to enroll. The Metavir score system will be used to interpret the liver biopsy and determine the fibrosis stage. In the absence of a liver biopsy, the equivalent Metavir score corresponding to the results of a screening FibroScan or FibroTest will be used to determine the baseline fibrosis stage as listed below:

Table 4. Baseline Fibrosis Stage

Baseline Fibrosis Stage, Metavir Equivalents	Liver Biopsy Metavir, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec Score	Liver Biopsy Ishak Score	FibroScan (kPa)	FibroTest
F0 – F1	0 or 1	0, 1, or 2	< 8.8	≤ 0.48
F2	2	3	≥ 8.8 to < 9.6	0.49 to 0.58
F3	3	4	≥ 9.6 to < 12.5	0.59 to 0.72
F3 or F4*	--	--	≥ 12.5 to < 14.6*	--
F4	4	5 or 6	≥ 14.6	≥ 0.73

* In the absence of a qualifying liver biopsy, subjects with a screening FibroScan result that is ≥ 12.5 kPa and < 14.6 kPa, a screening FibroTest result that is ≤ 0.72 and an APRI > 2, or a FibroTest result that is ≥ 0.73 and an APRI ≤ 2, should be evaluated based on the investigator's clinical judgment to determine the fibrosis stage (either F3 or F4).

The resulting Metavir score, as shown in the above table, will be documented via recording in the IRT system.

After meeting the eligibility criteria, subjects will be enrolled to either 12 or 24 weeks of treatment.

Figure 1. Study Schematic

This study will also utilize a Subject Care Plan Model. The Subject Care Plan Model is a mechanism that allows subjects to receive reminders for upcoming study visits, reminders to take study drugs, information about their HCV RNA values (if applicable) and/or receive disease specific education and encouragement at varying frequencies of contact.

Subjects will be contacted by a designated nurse educator, contracted by the sponsor, throughout the trial. The nurse educator may interact with subjects by phone, email, in-person visit, postal mail, text message or combinations of these listed communications to facilitate the assigned subject care plan level. After enrollment, the subjects will undergo a Subject Care Plan assessment (as part of Subject Care Plan Model) that will be conducted by a designated nurse educator. The care plan has three levels as detailed below:

> Care Plan Level 1: Subjects that are assessed as requiring a low level of support will be assigned to Care Plan Level 1 and will be contacted approximately 2 to 3 times per week.
>
> Care Plan Level 2: Subjects that are assessed as requiring a moderate level of support will be assigned to Care Plan Level 2 and will be contacted approximately 2 to 3 times per week and receive once daily study medication reminder.
>
> Care Plan Level 3: Subjects that are assessed as requiring a high level of support will be assigned to Care Plan Level 3 and will be contacted approximately 3 to 5 times per week and receive twice daily study medication reminders.

The designated nurse educator will assign a care plan level after their initial assessment and may adjust the care plan level as needed throughout the trial. The Subject Care Plan Model support will continue until subjects have completed their Post-Treatment Week 12 Visit. Details regarding Subject Care Plan Model are described in Section 5.3.1.1.

The study will consist of a Screening Period (Section 5.1.1), Treatment Period (Section 5.1.2) and a Post-Treatment Period (Section 5.1.3).

5.1.1 Screening

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study specific procedures, will receive a unique subject number via the Interactive Response Technology (IRT) system and will undergo the study procedures identified in Section 5.3.1 associated with the Screening Visit. The investigator or his/her designated and qualified representatives will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Study Day 1 prior to dosing and record the results of this assessment and the details of the informed consent process in the subject's medical records.

Eligible subjects have up to 42 days following the Screening Visit to enroll into the study.

5.1.1.1 Rescreening

Subjects who meet all eligibility criteria with the exception of up to three exclusionary laboratory parameters may rescreen once within the 42 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, 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 an exclusionary laboratory parameter(s) must have the laboratory parameter(s) repeated 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 (TP)

After meeting the eligibility criteria, subjects will be enrolled to either 12 or 24 weeks of treatment as described in Section 5.1 and Table 5.

HCV GT1-infected subjects who are either treatment-naïve or previously treated with IFN/RBV (IFN or pegIFN with RBV) will receive ABT-450/r/ABT-267 and ABT-333. Subjects with HCV GT1a infection and all GT1-infected subjects with compensated cirrhosis will receive RBV. The treatment duration will be 12 weeks for all subjects except HCV GT1a-infected subjects with compensated cirrhosis, who will receive treatment for 24 weeks unless a treatment duration of 12 weeks is selected by the investigator based on the subject's prior treatment history. Subjects will receive study drug regimens according to criteria listed in Table 5.

Table 5. Study Drug Regimen

Subject Population	Treatment Regimen*	Treatment Duration
Genotype 1a, without cirrhosis	ABT-450/r/ABT-267 + ABT-333 + ribavirin	12 weeks
Genotype 1a, with cirrhosis	ABT-450/r/ABT-267 + ABT-333 + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	ABT-450/r/ABT-267 + ABT-333	12 weeks
Genotype 1b, with cirrhosis	ABT-450/r/ABT-267 + ABT-333 + ribavirin	12 weeks

* Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

** Treatment for 12 weeks may be considered for some patients based on prior treatment history *(See response rates in GT1a cirrhotics by prior treatment history protocol Section 3.0, Table 1)*.

The site will enter subject's genotype (1b / Non-1b), fibrosis stage and prior IFN/RBV null responders and nonresponder information in the IRT system (Table 5).

ABT-450/r/ABT-267, ABT-333 and RBV (if applicable) will be administered as described in Section 5.5.1 (Treatments Administered). Subjects will receive instructions about the study at the Day 1 Visit. The study drugs will be dispensed at the visits indicated in Table 7.

After enrollment, all subjects will continue to return to the site on an outpatient basis for the study visits and procedures as identified in Table 7. Subjects could also return to the

site as an unscheduled study visit for additional safety visits if the investigator feels necessary. All subjects will be assigned to a care level based on the assessment as described in Section 5.3.1.1 (Subject Care Plan Model). Sites should ensure that subjects adhere to the study visits listed in Table 7. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

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

Virologic failure criteria will be evaluated and applied by the Investigator as detailed in Section 5.4.3.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Table 7 and as described in Section 5.3.1.1. Ideally, this should occur on the day of study drug discontinuation, but is recommended to be no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy if applicable. Following completion or premature discontinuation of study drug treatment, all subjects will enter the 260-week Post-Treatment Period.

The Treatment Period will assess safety, antiviral response, and clinical outcomes, including all-cause death, liver-related death, liver decompensation, occurrence of hepatocellular carcinoma, and liver transplantation.

5.1.3 Post-Treatment (PT) Period

All subjects who receive at least one dose of study drugs will enter into the Post-Treatment Period and return to the site on an outpatient basis for the study visits and procedures as identified in Table 7. The Post-Treatment Period will begin the day

following the last dose of study drug treatment and last for approximately 260 weeks as outlined in Table 7. Subjects could also return to the site as an unscheduled study visit for additional safety visits if the investigator feels necessary. Subjects who prematurely discontinue during the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit and undergo the study procedures as outlined in Table 7 and as described in Section 5.3.1.1.

All subjects will continue to receive the assigned subject care plan until the completion of Post-Treatment Week 12 Visit. Upon completion of Post-Treatment Week 12 Visit, all subjects in each care plan level will receive one final session with the nurse educator for final education. Details regarding Subject Care Plan Model are described in Section 5.3.1.1.

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

The post-treatment period will assess safety, antiviral response, and clinical outcomes, including all-cause death, liver-related death, liver decompensation, occurrence of hepatocellular carcinoma, and liver transplantation.

5.2 Selection of Study Population

The study population consists of HCV genotype 1-infected adult subjects with or without compensated cirrhosis, who are treatment-naïve or IFN/RBV (IFN or pegIFN with RBV) treatment-experienced.

Subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following 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)
   - sexually active with female partners only
   - not of childbearing potential, defined as:
     - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone (FSH) level indicating a postmenopausal state), or
     - surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s);
   - of childbearing potential and sexually active with male partner(s):
     - currently using at least one effective method of birth control at the time of screening and
     - agree 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), starting with Study Day 1 and for 30 days after stopping study drug or for 6 months after stopping study drug if receiving RBV (Note: Estrogen-containing hormonal contraceptives, including oral, injectable, implantable, patch and ring varieties, may not be used during study drug treatment).
3. Males who are not surgically sterile and 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) throughout the course of the study, starting with Study

Day 1 and for 30 days after stopping study drug or for 6 months after stopping study drug if receiving RBV.

4. Chronic HCV infection prior to study enrollment. Chronic HCV infection is defined as one of the following:
   - Positive for anti-HCV Ab or HCV RNA > 1,000 IU/mL at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
   - HCV RNA > 1,000 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).
5. Screening laboratory result indicating HCV genotype 1 infection.
6. 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 form, approved by an Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures.

Rationale for Inclusion Criteria

(1, 4, 5) To select the appropriate subject population with sufficient disease severity for evaluation.

(2, 3) RBV has known teratogenic effects. The impact of AbbVie DAAs on pregnancies is unknown.

(6) In accordance with harmonized Good Clinical Practice (GCP).

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. Women who are pregnant or breastfeeding.

2. Positive test result for Hepatitis B surface antigen (HbsAg) or confirmed positive anti-HIV antibody (HIV Ab) test.

3. Use of medications listed below, or medications contraindicated for ritonavir or RBV (for those that receive RBV), within 2 weeks or 10 half-lives whichever is longer, prior to study drug administration including but not limited to:

Table 6. Medications Contraindicated for Use with the Study Drug Regimen

Alfuzosin Astemizole Carbamazepine Dihydroergotamine Efavirenz Ergotamine Ergonovine	Estrogen-containing Medications for Systemic Use Fusidic Acid Gemfibrozil Lovastatin Methylergonovine Midazolam (oral) Phenobarbital	Phenytoin Pimozide Rifampin Sildenafil* Simvastatin St. John's Wort Terfenadine Triazolam

Not all medications contraindicated with 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.

* When used for the treatment of pulmonary arterial hypertension.

4. Use of known strong inducers of cytochrome P450 3A (CYP3A) or strong inducers of cytochrome P450 2C8 (CYP2C8) or strong inhibitors of CYP2C8 within 2 weeks of the respective medication/supplement, prior to initial dose of study drug.

5. Clinically significant abnormalities or co-morbidities, other than HCV infection that make the subject an unsuitable candidate for this study or treatment with RBV (if applicable) in the opinion of the investigator.

6. Current enrollment in another interventional clinical study, previous enrollment in this study, prior or current use of any investigational or commercially available anti-HCV agents other than IFN or RBV (including previous exposure to ABT-450, ABT-267 or ABT-333) or receipt of any investigational product within 6 weeks prior to study drug administration.

7. History of solid organ transplant.
8. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Creatinine Clearance (CrCl) < 30 mL/min as estimated by the Cockcroft-Gault equation:

     $$\text{CrCl} = [(140 - \text{Age}) \times \text{Mass (in kg)} \times (0.85 \text{ if female})] / [72 \times \text{Serum creatinine (in mg/dL)}]$$

   - Albumin < 2.8 g/dL
   - Hemoglobin < LLN
   - Platelets < 25,000 cells per mm^3
   - Total bilirubin > 3.0 mg/dL
9. Any current or past clinical evidence of Child-Pugh B or C Classification (Child-Pugh Score ≥ 7) or clinical history of liver decompensation such as ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.
10. Confirmed presence of hepatocellular carcinoma indicated on imaging techniques such as computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or on an ultrasound performed at Screening (a positive ultrasound result will be confirmed with CT scan or MRI).
11. HCV genotype performed during screening indicating infection with any genotype other than genotype 1.

Rationale for the Exclusion Criteria

(1) The impact of AbbVie DAAs on pregnancies is unknown.

(5, 7 – 10) To ensure safety of the subjects throughout the study.

(3, 4, 6) To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications.

(2, 11) To exclude subjects with viral infection other than HCV genotype 1.

5.2.3 Prior, Concomitant, and Prohibited 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 screening, 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.

During the Post-Treatment Period, all medications will be collected until 30 days following the last dose of study drugs. Only anti-HCV medications and concomitant medications relevant to SAE of death will be collected thereafter.

The AbbVie Study Designated Physician should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior Therapy

Subjects may be either treatment-naïve or IFN/RBV (IFN or pegIFN with RBV) treatment-experienced.

Prior or current use of any investigational or commercially available anti-HCV agents other than IFN or RBV, including telaprevir, boceprevir, sofosbuvir, simeprevir or an investigational agent, excludes a subject from this study. Subjects who previously participated in trials of investigational anti-HCV agents may be enrolled if they can produce documentation that they received only placebo.

5.2.3.2 Concomitant Therapy

Subjects must be able to safely discontinue any prohibited medications within 2 weeks or 10 half-lives of the medication, whichever is longer, prior to initial study drug administration and through 2 weeks following discontinuation of study drugs. Subjects

must review and sign an Informed Consent form prior to discontinuing any prohibited medications for the purpose of meeting study inclusion criteria.

The investigator or a qualified designee should confirm that a 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. The investigator or qualified designee should review concomitant medication(s) label(s) and should also utilize the drug-drug interactions (DDI) tool that will be provided by the sponsor to screen concomitant medications at each visit for potential drug-drug interactions (DDI) with study drugs. The site should document their DDI review in the source or print report and maintain it in the subject's study files.

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.

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 30 days after stopping study drug or for 6 months after stopping study drug if receiving RBV. Subjects using systemic estrogen-containing medications (including estrogen containing oral contraceptives) have a higher risk for elevated ALT levels. Subjects using these kinds of medications must discontinue them at least 2 weeks prior to initial 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.

During the Post-Treatment Period, investigators should reassess concomitant medications. Subjects may revert to pre-study doses, at a minimum of 2 weeks following discontinuation of study drugs, if applicable.

5.2.3.3 Prohibited Therapy

In addition to the medications listed in Table 6, use of known strong inducers of CYP3A or strong inhibitors or inducers of CYP2C8 is prohibited within 2 weeks or 10 half-lives of the medication, whichever is longer, prior to the initial dose of study drugs and through the first 2 weeks after the subject has completed study drugs in the Treatment Period.

The investigator or a qualified designee should refer to the RBV labeling and DDI tool that will be provided by the sponsor for a list of prohibited medications. The site should document their DDI review in the source or print report and maintain it in the subject's study files. Anti-HCV medications other than those specified in the protocol will not be allowed during the Treatment Period of the study.

Subjects must be able to safely discontinue any prohibited medications. Subjects must be consented prior to discontinuing any prohibited medications for the purpose of meeting study inclusion criteria. During the Post-Treatment Period, investigators should reassess prohibited medications and subjects may resume previously prohibited medications or revert to pre-study doses, at a minimum of 2 weeks following discontinuation of study drugs, if applicable.

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 7. Study Activities

Activity	Screening	Day 1[a]	Week 2	Week 4	Week 12[b]	End of Treatment (EOT) (Week 12 or 24) or Treatment D/C[b,c]	Post-Treatment Wks 4, 12, 24, 52, 104, 156, 208, 260 or PT Treatment D/C
Informed Consent[d]	X						
Provide RBV Medication Guide[e]	X						
Medical History	X	X[f]					
Physical Exam[g]	X	X					
ECG	X						
Vital Signs, Weight and Height	X[h]	X	X	X	X	X	X
Pregnancy Test [serum (s) urine (u)][i]	X (s)	X (u)		X(u)	X(u)	X(u)	X(u)
Hematology/Chemistry/Urinalysis/ Coagulation Panel	X	X	X	X	X	X	X[j]
FSH (all females)	X						
HBsAg, Anti-HCV Ab, Anti-HIV Ab	X						
HCV Genotype and Subtype	X						
IL28B Sample	X						
Child-Pugh Score[k]	X						
Liver ultrasound[l]	X					X	X
Concomitant Medication Assessment[m]	X	X	X	X	X	X	X[n]

Table 7. Study Activities (Continued)

Activity	Screening	Day 1[a]	Week 2	Week 4	Week 12[b]	End of Treatment (EOT) (Week 12 or 24) or Treatment D/C[b,c]	Post-Treatment Wks 4, 12, 24, 52, 104, 156, 208, 260 or PT Treatment D/C
Adverse Event Assessment	X	X	X	X	X	X	X[n]
Study Drugs Dispensation		X		X	X[o]		
Subject Care Plan Model[p]	X	X	X	X	X	X	X[q]
HCV RNA Samples	X	X	X	X	X	X	X
Assignment of Subject Numbers via IRT	X						
Enrollment		X					
HCV Resistance Sample		X	X	X	X	X	X
Archive Samples (Plasma & Serum)		X	X	X	X	X	X
Study Drug Returned for IRT Reconciliation				X	X	X[b]	
Liver Biopsy, FibroScan or FibroTest for liver fibrosis assessment[r]	X	X[r]					X[r]
Patient Reported Outcome (SF-36v2 and FACIT–F)[s]		X		X	X	X	X
Assessment of Clinical Outcomes[t]			X	X	X	X	X
Clinical Assessment of Liver Decompensation[k]		X					
Total Insulin		X			X	X	X[u]

Wk = Week; D/C = Discontinuation; EOT (End of Treatment) = Final Treatment Visit; Day 1 = Baseline Visit

Table 7. Study Activities (Continued)

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

b. Treatment Duration Study Visits:
   - Subjects assigned to 12 weeks of treatment will complete the procedures and return drug from the screening visit through the EOT Week 12/ D/C visit procedures. Subjects will complete EOT Week 12 visit procedures instead of completing a Week 12 visit.
   - Subjects assigned to 24 weeks of treatment will complete the procedures and return drug from the screening visit through the EOT Week 24/ D/C visit procedures at Week 24. Subjects will complete a Week 12 Study Visit as an interim visit.
   - Study drug returned for IRT Reconciliation at Week 24 is only applicable to subjects who will receive treatment for 24 weeks.

c. Subjects that prematurely discontinue from the Treatment Period should return to the site to complete the Final/Treatment D/C visit procedures.

d. Subjects will need to sign an informed consent for the study (prior to performing any screening or study-specific procedures).

e. Where applicable/locally available.

f. Medical history will be updated at the Day 1 Visit prior to study drug administration. This updated medical history will serve as the Baseline for clinical assessment.

g. A symptom-directed physical examination may be performed at any other visit, when necessary

h. Height will be measured at screening visit only.

i. Serum/Urine pregnancy testing is not required 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. (Refer to Section 5.3.1.1) [Pregnancy Test] for additional details.) Females of childbearing potential who are receiving RBV should have urine pregnancy testing done monthly starting from Day 1 (Baseline) through 6 months after RBV discontinuation. Females of childbearing potential who are receiving DAA only should have urine pregnancy testing done thru Post-Treatment Week 4.

j. Urinalysis will not be conducted after the Post-Treatment Week 4.

k. Applies only to subjects with cirrhosis. The Child-Pugh score will be calculated in the EDC RAVE system. Subjects who were considered to be non-cirrhotic at the Screening visit but identified as cirrhotic (according to definitions listed in Section 5.1) during the screening period will return to the site prior to the baseline visit for Child-Pugh assessment.

l. For subjects with compensated cirrhosis:
   - Subjects receiving 12 weeks of treatment will have a liver ultrasound performed at the screening visit and all Post-Treatment visits except Post-Treatment Week 4.
   - Subjects receiving 24 weeks of treatment will have a liver ultrasound performed at the screening visit, Week 24 visit, and all Post-Treatment visits except the Post-Treatment Week 4 and Post-Treatment Week 12.
   - Subjects with a historical negative liver ultrasound, CT or MRI (within 3 months prior to screening) are not required to undergo a screening ultrasound.

Table 7. Study Activities (Continued)

For subjects without cirrhosis: Liver ultrasound will be performed at the screening visit, Post-Treatment Week 52, Post-Treatment Week 156 and Post-Treatment Week 260. Subjects with a historical negative liver ultrasound, CT or MRI (within 3 months prior to screening) are not required to undergo a screening ultrasound.

m. The DDI tool provided by the sponsor should be utilized to evaluate concomitant medications for potential drug-drug interaction (DDI).

n. AEs and concomitant medications will not be collected after the Post-Treatment Week 4 visit. Only anti-HCV medications and concomitant medications relevant to SAE of death will be collected after the Post-Treatment Week 4 visit.

o. Study drugs only dispensed at Week 12 for subjects who will receive treatment for 24 weeks.

p. Procedures related to Subject Care Plan Model are detailed in Section 5.3.1.1 [Subject Care Plan Model].

q. Subject Care Plan will end after Post-Treatment Week 12 Visit. Upon completion of Post-Treatment Week 12 Visit, all subjects in each care plan level will receive one final session with the nurse educator for final education.

r. Historical or screening liver biopsy, FibroScan or FibroTest results will be used to determine the presence or absence of cirrhosis for the purpose of treatment assignment. Fibrotest will be performed at Day 1, PT Week 12 during the post-treatment period.

s. SF-36v2 and FACIT–F should be administered as of the first study procedure at each visit and in the order listed.

t. Clinical Outcome events that occur during the Treatment Period through Post-Treatment Week 4 are to be recorded and documented in the eCRF as an AE/SAE in addition to being captured in the Clinical Outcome eCRF(s). Clinical outcome events that occur after Post-Treatment Week 4 are to be recorded in the Clinical Outcome eCRFs only, except when the clinical outcome is death, in which case the SAE eCRF would also need to be completed.

u. Total insulin will be collected at all scheduled Post-Treatment visits except PT Week 4, PT Week 12 and PT Week 24.

5.3.1.1 Study Procedures

The study procedures outlined in Table 7 are discussed in detail in this section with the exception of the assessment of concomitant medications (Section 5.2.3), and the collection of adverse event information (Section 6.4). All study data will be recorded in the subject's source documentation and then on the appropriate eCRFs, with the exception of laboratory data which will be provided to the Sponsor electronically from the 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 taking RBV 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, nicotine containing products and alcohol use, will be taken from each subject during the Screening Visit. An updated medical history will be obtained prior to study drug administration and will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Table 7. 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, blood pressure, pulse and body weight will be measured at the visits specified in Table 7, or upon subject discontinuation. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The vital signs performed on Study Day 1 will serve as the baseline for clinical assessment. 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 the Screening visit and will serve as the baseline assessment. The ECG should be performed prior to blood collection.

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

Normal ECG

Abnormal ECG – not clinically significant

Abnormal ECG – clinically significant

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

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 8 at the visits indicated in Table 7.

Blood samples for serum chemistry tests should ideally be collected following a minimum 8-hour fast at the following visits: Day 1, Final Treatment Visit, and PT Week 52, 104, 156, 208, and 260. The remaining visits may be non-fasting.

Subjects whose visits occur prior to the morning dose of study drug should be instructed to fast after midnight. Subjects whose visits occur following the morning dose of study drug should be instructed to fast after breakfast until the study visit occurs.

At the Day 1 study visit, a fasting blood sample is to be collected prior to the first dose of study drug which is administered at the Day 1 study visit. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Subjects should be reminded to eat prior to their first dose of study drug (e.g., suggest they bring a light snack). Fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is ICON. Samples will be sent to the following address:

ICON Central Laboratories
123 Smith Street
Farmingdale, NY 11735 USA

Table 8. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Additional Tests
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands, if detected Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) ANC Prothrombin Time/INR[a] Activated partial thromboplastin time (aPTT) Reticulocyte count	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin[a,d] 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[a] Chloride Bicarbonate Magnesium Gamma-glutamyl transferase (GGT)[d] Creatinine clearance (Cockcroft Gault calculation) Alpha2-macroglobulin[d] Haptoglobin[d] Apolipoprotein A1[d]	HBsAg[b] Anti-HCV Ab[b] Anti-HIV Ab[b] FSH (all females)[b] Urine and Serum Human Chorionic Gonadotropin (hCG) females)[c] HCV RNA IL28B[b] HCV genotype and subtype[b] Total Insulin
Urinalysis		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Microscopic (reflex)		

a. Also a component of the Child-Pugh Assessment.

b. Performed only at Screening.

c. Serum and urine pregnancy testing is not required 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.

d. Also a component of FibroTest.

Pregnancy Test

Serum and urine pregnancy tests are not required for female subjects with documented prior bilateral tubal ligation, bilateral oophorectomy or hysterectomy or for subjects who are confirmed to be postmenopausal.

Confirmation of postmenopausal status measured by FSH will be obtained at the Screening Visit only for all female subjects.

For females of childbearing potential:

- A serum pregnancy test will be performed at the Screening visit only and analyzed by the central laboratory.
- Pregnancy testing will be performed as specified in Table 7 regardless of treatment regimen.
- Subjects that receive a RBV containing regimen will have pregnancy tests performed monthly throughout the Treatment Period and for a minimum of 6 months after the discontinuation of RBV, or according to the local RBV label and/or local treatment guidelines for RBV.
- Urine pregnancy testing will be performed on-site during the study visit if there is a scheduled visit. If there is not a scheduled study visit, subjects may either have pregnancy testing performed at the site as an unscheduled study visit or a urine pregnancy test may be conducted by the subject at home with a pregnancy test kit provided by the site. If a urine pregnancy test is performed at home, site personnel should contact these female study subjects to capture the results of any study-related pregnancy tests in the source records only.
- If a urine pregnancy result is positive, a confirmatory hCG serum test should be collected and sent to the central lab.

Concomitant Medication Assessment

Use of medications (prescription or over-the-counter, including vitamins and herbal supplements) from the time of signing the consent through 30 days after last dose of study drug will be recorded in the eCRF at each study visit indicated in Table 7. During the

Post-Treatment Period, all medications will be collected until 30 days following the last dose of study drugs. Only anti-HCV medications and concomitant medications relevant to SAE of death will be collected thereafter as indicated in Table 7. The investigator or his/her designated and qualified representatives should review concomitant medication(s) label(s) and should also utilize the DDI (drug-drug interactions) tool that will be provided by the sponsor to screen concomitant medications at each visit for potential drug interaction with study drugs. The site should document their DDI review in the source or print report and maintain it in the subject's study. The sites should refer to Section 5.2.3 (Prior, Concomitant, and Prohibited Therapy).

Hepatitis and HIV Screen

HBsAg (hepatitis B surface antigen), anti-HCVAb and anti-HIV Ab will be performed at Screening. A positive anti-HIV Ab test must be confirmed. The investigator or his/her representatives must discuss any local reporting requirements to local health agencies with the subject. The site will report these results per local regulations, if necessary.

HCV Genotype and Subtype

Plasma samples for HCV genotype and subtype will be collected at Screening. Genotype and subtype will be assessed using the Central lab.

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Table 7 and analyzed using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0. For this assay, the lower limit of quantification (LLOQ) is 15 IU/mL.

Liver Biopsy, FibroScan or FibroTest

At Screening, subjects should meet all of the inclusion criteria and none of the exclusion criteria before undergoing a liver biopsy if a historical biopsy is not available.

Subjects who have not had a liver biopsy within 24 months prior to screening, but who otherwise meet all of the inclusion criteria and none of the exclusion criteria will undergo either a liver biopsy or non-invasive test (FibroScan or FibroTest/APRI prior to enrollment) to determine presence or absence of cirrhosis. **APRI should be calculated from samples drawn on the same day.** Selection of liver biopsy or non-invasive testing should be based on local standard practice.

FibroTest will be performed as indicated in Table 7.

Child-Pugh Score and Category

The Child-Pugh score will be calculated and documented at the Screening Visit for Cirrhotic subjects only. Subjects who were considered to be non-cirrhotic at screening visit but identified as cirrhotic (according to definitions listed in Section 5.1) during the screening process will return to the site prior to the baseline visit for Child-Pugh assessment.

The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments). Child-Pugh score will be determined at the screening visit as indicated in Table 7. The Child-Pugh score will be automatically calculated prior to Day 1 by EDC RAVE once the investigator or designated site personnel enters the subject's parameters (as listed in Table 9). A total score of 5 – 6 is considered Class A (compensated disease); 7 – 9 is Class B (significant functional compromise); and 10 – 15 is Class C (decompensated disease).

Table 9. Child-Pugh Classification of Severity of Cirrhosis

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

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

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

Clinical Assessment of Liver Decompensation

A clinical assessment of hepatic encephalopathy and ascites will be performed at Study Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since screening for all subjects who have compensated cirrhosis. Grading system guidelines for ascites are listed above in Table 9.

Hepatocellular Carcinoma Screening: Liver Ultrasound

In order to monitor for the presence of hepatocellular carcinoma (HCC), an ultrasound of the liver will be performed as indicated in Table 7.

For subjects with compensated cirrhosis:

- Subjects receiving 12 weeks of treatment will have a liver ultrasound performed at the screening visit and all Post-Treatment visits except Post-Treatment Week 4
- Subjects receiving 24 weeks of treatment will have a liver ultrasound performed at the screening visit, Week 24 visit, and all Post-Treatment visits except the Post-Treatment Week 4 and Post-Treatment Week 12.

For subjects without cirrhosis: Liver ultrasound will be performed at the Screening Visit, Post-Treatment Week 52, Post-Treatment Week 156 and Post-Treatment Week 260.

Subjects with a historical negative liver ultrasound, CT or MRI (within 3 months prior to screening) are not required to undergo a screening ultrasound.

A positive Ultrasound result suspicious for HCC during the treatment or post-treatment period will be confirmed with CT scan or MRI.

Assessment of Clinical Outcomes

The following clinical outcomes will be assessed during the study at visits outlined in Table 7:

- All-cause death: Death due to any cause.
- Liver-related death: Death as the result of a liver-related cause, based on the opinion of the clinical site principal investigator.
- Liver transplantation: Any subject who had undergone liver transplantation.
- Liver decompensation: Development of any of the following conditions: ascites, hepatic encephalopathy, or variceal bleeding.
- Hepatocellular carcinoma (HCC): Any subject in whom, at any time during the study, HCC developed. HCC is defined by histologic confirmation or a > 1 cm mass lesion on cross-sectional imaging that meets the diagnostic criteria of HCC according to AASLD guidelines.[30]

- Composite of any of the above outcomes.

Clinical Outcome events that occur during the Treatment Period through Post-Treatment Week 4 are to be recorded and documented in the AE/SAE eCRF (Section 6.0) in addition to being captured in the Clinical Outcome eCRF. Clinical Outcome events that occur after Post-Treatment Week 4 are to be recorded in the Clinical Outcome eCRFs only, except when the clinical outcome is death, in which case the SAE eCRF would also need to be completed.

An independent outcome committee will review and adjudicate the validity of each clinical outcome as per the charter.

HCV Resistance Testing Plasma Sample

A plasma sample for HCV resistance testing will be collected at the study visits, indicated in Table 7. Specific instructions for preparation and storage of the samples will be provided by the central laboratory, the Sponsor, or its designee.

Subject Care Plan Model

The Subject Care Plan model is a mechanism that allows subjects to receive reminders for upcoming study visits, reminders to take study drugs, information about their HCV RNA values (if applicable) and/or receive disease specific education and encouragement at varying frequencies of contact.

Subjects will be contacted by a designated nurse educator, contracted by the sponsor, throughout the trial. The nurse educator may interact with subjects by phone, email, in-person visit, postal mail, text message or combinations of these listed communications to facilitate the assigned subject care plan level.

The investigator or his/her designated site personnel will register each subject in the web-based care model portal after enrollment. However, if the web-based portal is not operable, or the site information is not available in the portal, the nurse educator may obtain this information verbally from the site. The subject profile form will collect broad

demographic information, including but not limited to, the subject's contact information and best time of contact.

Once the subject profile is registered, the subject will be contacted after enrollment by the nurse educator, for administration of a brief care plan assessment that will be approximately 10 to 30 minutes in duration.

The nurse educator will make three contact attempts and if possible, will leave a voice message requesting the subject to call them back and/or allow the subject to also leave a voice message for the nurse educator. If the subject cannot be reached after three attempts, the investigator or his/her designated site personnel will be notified and the nonresponsive subject will be assigned to care level 1 by the nurse educator. Subjects who do not have access to internet or do not have email will be contacted by phone or postal mail.

After the completion of initial assessment, the nurse educator will assign each subject to one of the three care plan levels that may be adjusted throughout the trial dependent upon subject responsiveness, needs or request of the subject. Each care plan level provides varying levels of support as outlined below for subjects during study drug treatment and will continue until the subject has completed Post-Treatment Week 12 Visit.

Subject Care Plan Levels:

Care Plan Level 1: Subjects that are assessed as requiring a low level of support will be assigned to Care Plan Level 1 and will be contacted approximately 2 to 3 times per week.

Care Plan Level 2: Subjects that are assessed as requiring a moderate level of support will be assigned to Care Plan Level 2 and will be contacted approximately 2 to 3 times per week and receive once daily study medication reminder.

Care Plan Level 3: Subjects that are assessed as requiring a high level of support will be assigned to Care Plan Level 3 and will be contacted approximately 3 to 5 times per week and receive twice daily study medication reminders.

Investigative site personnel will be notified of any subjects that cannot be reached after approximately two phone call attempts to perform any necessary follow-up (confirm subject status, verify contact information, etc.). The site may enter subjects' scheduled visit dates, actual visit dates, concomitant medication, and treatment duration into the web-based portal. The nurse educators or site personnel may use the web-portal as a resource to confirm that the subject is taking their AM and PM doses.

Upon completion of the Post-Treatment Week 12 Visit, all subjects in each care level will receive one final session with the nurse educator for final education.

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 7. 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 or understand any of the instruments may have site personnel read the questionnaires to them. Site personnel will encourage completion of each instrument at all applicable visits and will ensure that a response is entered for all items.

In this study, PRO instruments will be consistently presented so that subjects will complete the Short-Form 36 Version 2 health survey (SF-36v2) instrument first, and the FACIT–F instrument second. PRO instruments should be completed as of the first study procedure at each visit and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

Short Form 36 – Version 2 Health Survey (SF-36v2)

The SF-36v2 is a non-disease specific Health Related Quality of Life (HRQoL) instrument with extensive use in multiple disease states. The SF-36v2 instrument comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality,

social functioning, role emotional and mental health) with a recall period of 4 weeks. Domain scores are aggregated into a Physical Component Summary score and a Mental Component Summary score. Higher SF-36v2 scores indicate a better state of health. Completion of the SF-36v2 should require approximately 10 minutes.

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT–F)

The FACIT–F is a symptom specific instrument with a focus on measuring fatigue in a variety of chronic diseases or health conditions. It was originally developed from interviews with oncology patients and clinical experts to assess anemia-associated fatigue. Its 13-item-version assesses peripheral, central, or mixed fatigue with a recall period of 7 days and yields a summed total score ranging between 0 and 52. Higher FACIT–F scores indicate a lesser degree of fatigue. Completion of the FACIT–F (version 4) should require approximately 5 – 10 minutes.

Assignment of Subject Numbers

A subject number is assigned at screening via IRT. Screening numbers will be unique 4-digit numbers and will begin with 1001, with the first 2 digits representing the investigative site and the last 2 digits representing the subjects at that site. Enrolled subjects will keep their screening number as their subject number.

Study Drug Dispensation

Study drugs will be dispensed at the visits as indicated in Table 7.

Study Drug Returned for IRT Reconciliation

At each visit noted in Table 7, the number of tablets of ABT-450/r/ABT-267, ABT-333, and RBV (if applicable) remaining in each kit (blister card for DAAs or bottle for RBV) will be entered into the IRT system. Additional information regarding treatment compliance can be found in Section 5.5.6.

Archive Samples

Archive plasma and serum samples will be collected at the study visits, indicated in Table 7. 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, biomarkers of inflammation, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by the Sponsor.

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

5.3.1.2 Blood Samples for Pharmacogenetic Analysis

IL28B Sample

One (required) 4mLwhole blood sample for deoxyribonucleic acid (DNA) isolation will be collected from each subject at screening for Interleukin 28B (IL28B) pharmacogenetic analysis and related markers. If the sample is not collected at this visit, it may be collected at any time throughout the study. This sample will not be used for any testing other than IL28B genotypes.

Specific instructions for sample collection and storage will be provided by the central laboratory, the Sponsor, or its designee. Samples will be used only for IL-28B testing and then destroyed.

5.3.1.3 Meals and Dietary Requirement

All study drugs should be dosed together and administered with food, i.e., the morning dose of ABT-450/r/ABT-267, ABT-333 and RBV(if applicable) should be taken together with food and the evening dose of ABT-333 and RBV (if applicable) should be taken together with food.

5.3.2 Efficacy Variables

5.3.2.1 Primary Variable

The primary endpoint is the incidence of all-cause death, liver-related death, liver decompensation, liver transplantation, hepatocellular carcinoma, and the composite of any of the above outcomes observed during the post-treatment period.

5.3.2.2 Secondary Variables

The secondary endpoints are:

- The percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug);
- The mean change from baseline in quality of life and fatigue to Post-Treatment Week 12 and Post-Treatment Week 24 (assessed by Short Form 36 Version 2 health survey (SF-36v2) and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT–F) questionnaires.
- Adherence to the prescribed regimen (measured by pill counts for each type of tablet).

5.3.3 Safety Variables

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

5.3.4 Pharmacogenetic Variable

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 ABT-450, ABT-267, ABT-333, or drugs of these classes. The results may also be used for the development of diagnostic tests related to IL28B and study treatment, or drugs of these classes.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

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

Subjects that discontinue study regardless of cause should be contacted (minimally as a telephone assessment) at each scheduled yearly visit to collect the survival status only if they provide consent. Details regarding informed consent are provided in Section 9.3.

If the subject prematurely discontinues during the Treatment Period or the Post-Treatment Period, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 7. Ideally for study drug discontinuation, this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment. The last dose of any study drug and reason for discontinuation from the Treatment Period will be recorded in the EDC (electronic data capture) system.

If a subject has an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range at the time of study drug discontinuation, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the Treatment Period, the administration of RBV (if applicable) to that subject must be discontinued immediately and DAAs may be continued

at the principal investigator's discretion after discussion with the subject, if the benefit of continuing DAAs is felt to outweigh the potential risk. Specific instructions regarding subject pregnancy can be found in Section 6.6. Subjects will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.2. The investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry, if applicable.

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 and subsequently provide written instructions for study termination.

5.4.3 Discontinuation of Subjects Meeting Virologic Failure Criteria

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;
- 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 while on DAA therapy, the subject will discontinue study treatment as described above. If the investigator believes the virologic failure is due to study drug interruption and/or is compliance related, the AbbVie Study Designated Physician should be contacted to discuss alternative management.

5.5 Treatments

5.5.1 Treatments Administered

ABT-450/r/ABT-267 will be provided by the Sponsor as 75 mg/50 mg/12.5 mg tablets. ABT-450/r/ABT-267 will be taken orally as 2 tablets once daily which corresponds to a ABT-450 150 mg/ritonavir 100 mg/ABT-267 25 mg dose. ABT-333 will be provided by the Sponsor as 250 mg tablets. ABT-333 will be taken orally as 1 tablet twice daily, which corresponds to a 250 mg dose BID.

RBV will also be provided as 200 mg tablets. Ribavirin is dosed based on weight, 1000 to 1200 mg divided twice daily per local label. For example, for subjects weighing < 75 kg, RBV may be taken orally as 2 tablets in the morning and 3 tablets in the evening which corresponds to a 1000 mg total daily dose. For subjects weighing ≥ 75 kg, RBV may be taken orally as 3 tablets in the morning and 3 tablets in the evening which corresponds to a 1200 mg total daily dose.

For subjects with CrCl ≥ 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 13).

5.5.2 Identity of Investigational Products

Table 10. Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
ABT-450/ritonavir/ABT-267	AbbVie	Oral	Tablet	75 mg/50 mg/ 12.5 mg
ABT-333	AbbVie	Oral	Tablet	250 mg
Ribavirin	Generic Manufacturer	Oral	Tablet	200 mg

All study drugs should be dosed together and administered with food as described in Section 5.3.1.3 (Meals and Dietary Requirement).

5.5.2.1 Packaging and Labeling

ABT-450/r/ABT-267 and ABT-333 tablets will be supplied in weekly kits. Each kit will consist of a blister card containing 1 week of study medication plus one additional day of drug. There will be 16 ABT-333 250 mg tablets and 16 ABT-450/r/ABT-267 75 mg/ 50 mg/12.5 mg tablets for a total of 32 tablets per blister card.

The blister cards indicate which drugs on the card should be taken in the morning (both ABT-450/r/ABT-267 tablets and one ABT-333 tablet) with a picture of a sun and which should be taken in the evening (one ABT-333 tablet) with a picture of a moon.

Ribavirin tablets will be supplied to the site in bottles containing 168 tablets.

All study drugs will be labeled as required per country requirements.

The labels must remain affixed to the primary and potential secondary packaging material. All blank spaces should be completed by site staff prior to dispensing to subject.

5.5.2.2 Storage and Disposition of Study Drugs

Table 11. Study Drug Storage Conditions

Study Drug	Storage Conditions
ABT-450/r/ABT-267 and ABT-333 blister cards	15° to 25°C (59° to 77°F)
Ribavirin bottles	15° to 25°C (59° to 77°F)

The investigational products are for investigational use only and are to be used only within the context of this study. The study drugs 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 the Sponsor. Upon receipt of study drugs, the site will acknowledge receipt within the IRT system.

5.5.3 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, all subjects will be assigned a unique subject number through the use of IRT. For subjects who do not meet the study selection criteria (or who are unable to enroll before enrollment has closed), the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study on Study Day 1. 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 kit numbers. The study drug kit numbers will be assigned according to schedules computer-generated before the start of the study by the AbbVie Data and Statistical Sciences Department.

Contact information and user guidelines for IRT use will be provided to each site. Upon receipt of study drugs, the site will acknowledge receipt in the IRT system.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.5.1. Study drug dosing will be initiated at the Study Day 1 Visit. ABT-450/r/ABT-267 will be dosed QD and ABT-333 will be dosed BID. Thus with normal dosing, 2 ABT-450/r/ABT-267 tablets and 1 ABT-333 tablet should be taken in the morning, and 1 ABT-333 tablet should be taken in the evening. RBV (if applicable) will be dosed BID.

All study drugs should be dosed together and administered with food at approximately the same times in the morning every day, i.e., the AM dose of ABT-450/r/ABT-267, ABT-333 and RBV (if applicable) should be taken together with food and the PM dose of ABT-333 and RBV (if applicable) should be taken together and 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 those described in the protocol.

All study drugs will be dispensed to 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. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs.

During the Treatment Period, subjects will be instructed to bring all study drug kits (full, partial or empty) to the study site at each study visit. The study site personnel will inspect the contents of the bottles and blister cards at Study Visits defined as Study Drug Returned for IRT Reconciliation in Table 7 and record the status of each one as well as

the exact number of remaining tablets of ABT-450/r/ABT-267 and ABT-333 or tablets of RBV (if applicable) and the date of reconciliation in the IRT system. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

5.5.7 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts using the IRT system. A current (running) and accurate inventory of study drug will be kept by the investigator or his/her designated and qualified representatives and will include lot number, number of tablets dispensed, subject number, username of person who dispensed study drug and date dispensed for each subject. Final accountability will be verified by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug kit, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the kit is damaged, the subject will be requested to return the remaining study drug to the site. Replacement study drug may only be dispensed to the subject by contacting the IRT system. Study drug replacement(s) and an explanation of the reason for the misplaced or damaged study drug(s) will be documented within the subject source documentation. Study drug start dates for each drug and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each kit, number of tablets remaining in each one returned, and the date of reconciliation will be documented in the IRT system at Study Visits defined as Study Drug Returned for IRT Reconciliation in Table 7. The monitor will review study drug accountability on an ongoing basis.

Upon completion of or discontinuation from the Treatment Period, all original study drug bottles (containing unused study drugs) will be returned to the Sponsor (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability

procedures. The number of tablets of each type of study drug returned in each kit 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 Groups

The combination regimen of ABT-450/r/ABT-267 and ABT-333 with or without RBV for 12 and 24 weeks has been evaluated in treatment-naïve and pegIFN/RBV treatment-experienced HCV GT1-infected subjects, with or without compensated cirrhosis, in the Phase 3 studies. Based upon the results from Studies M11-646, M13-098, M13-961, M13-389, M14-002 and M13-099 (discussed in detail in Section 3.0), AbbVie plans to evaluate the same combination regimen used in the Phase 3 studies in a study population of treatment-naïve and IFN/RBV treatment-experienced HCV GT1-infected subjects, with or without compensated cirrhosis. The intention of this study is to assess the effect of treatment response on long-term clinical outcomes and evaluate the SVR_{12} following treatment with ABT-450/r/ABT-267 and ABT-333, with or without RBV. Given the above considerations, it is anticipated that the study design will maximize the SVR rates in the population. As such, the absence of randomization, blinding and control groups is appropriate. No hypothesis testing is planned; statistical analyses will be descriptive.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA assays are standard and validated. The SF-36v2 and FACIT–F instruments are standard in the literature and thoroughly validated in the general population and in subjects who have chronic health conditions. The SF-36v2 health survey is the standard Health-related Quality of Life instrument in hepatitis C subjects worldwide and FACIT–F has been used in hepatitis C registration clinical trials as an assessment tool for fatigue.

5.6.3 Suitability of Subject Population

This study plans to enroll both HCV treatment-naïve and IFN/RBV treatment-experienced subjects with genotype 1 chronic HCV, with or without compensated cirrhosis. The subject population to be studied is reflective of the current demographics of chronic HCV infection in the United States. Moreover, this study population has been evaluated in the phase 3 studies where more than 2,300 subjects received the combination regimen that is planned to be administered in this study. In the Phase 3 studies, treatment with ABT-450/r/ABT-267 and ABT-333 with RBV for 12 weeks resulted in SVR_{12} in 96% to 99% of HCV GT1-infected, treatment-naïve subjects without cirrhosis, and 96% to 100% of HCV GT1-infected, pegIFN/RBV treatment-experienced subjects without cirrhosis. Similarly, high SVR_{12} rates (99% to 100%) were seen in HCV GT1b-infected treatment-naïve and pegIFN/RBV treatment-experienced subjects without cirrhosis following treatment with ABT-450/r/ABT-267 and ABT-333, without RBV for 12 weeks. Among subjects with compensated cirrhosis, 92% and 96% of HCV GT1-infected treatment-naïve and pegIFN/RBV treatment-experienced subjects achieved SVR_{12} following treatment with ABT-450/r/ABT-267 and ABT-333 with RBV for 12 and 24 weeks, respectively. The DAA regimen ABT-450/r, ABT-267 and ABT-333 with or without RBV have been well tolerated in the Phase 3 studies, as evidenced by the low rate of treatment discontinuation and serious adverse events.

5.6.4 Selection of Doses in the Study

ABT-450/r/ABT-267 and ABT-333:

Doses of the three DAAs to be used in this study have been administered in the Phase 3 Studies M11-646, M13-098, M13-389, M13-961, M14-002 and M13-099 have shown high SVR_{12} rates in combination with each other, with or without RBV, with a favorable safety profile. The maximum dose of ABT-450/r/ABT-267 75 mg/50 mg/12.5 mg tablets will not exceed 150 mg/100 mg/25 mg per day for 24 weeks. The maximum dose of ABT-333 250 mg tablets administered in this study will not exceed 500 mg per day for 24 weeks.

RBV

The daily dose of RBV (if applicable) in this study is 1000 or 1200 mg, divided twice daily, and based on subject weight. This dose is approved for treatment of adult patients with chronic hepatitis C infection in combination with pegIFN. The same dose was studied in the Phase 3 Studies M11-646, M13-098, M13-389, M13-961, M14-002 and M13-099 and was found to be generally safe and well tolerated and resulted in high SVR rates.

The maximum RBV dose administered in this study will not exceed 1200 mg, divided twice daily for 24 weeks.

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 related to 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 or 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.

Protocol-defined clinical outcomes consist of:

- All-cause death: Death due to any cause.
- Liver-related death: Death as the result of a liver-related cause, based on the opinion of the clinical site principal investigator.
- Liver transplantation: Any subject who had undergone liver transplantation
- Liver decompensation: Development of any of the following conditions: ascites, hepatic encephalopathy, or variceal bleeding.
- Hepatocellular carcinoma (HCC): Any subject in whom, at any time during the study, HCC developed. HCC is defined by histologic confirmation or a ≥ 1 cm mass lesion on cross-sectional imaging meets the diagnostic criteria of HCC according to AASLD guidelines.[30]

Clinical Outcome events that occur during the Treatment Period through Post-Treatment Week 4 are to be recorded and documented in the eCRF as an AE/SAE in addition to being captured in the Clinical Outcome eCRF(s). Clinical Outcome events that occur after Post-Treatment Week 4 are to be recorded in the Clinical Outcome eCRFs only, except when the clinical outcome is death, in which case the SAE eCRFs would also need to be completed.

These outcomes will form part of the study endpoints and will be reported in the clinical study report at the end of the study.

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 serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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 DAAs (ABT-450/r/ABT-267 and ABT-333) and to the use of RBV (if applicable):

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.

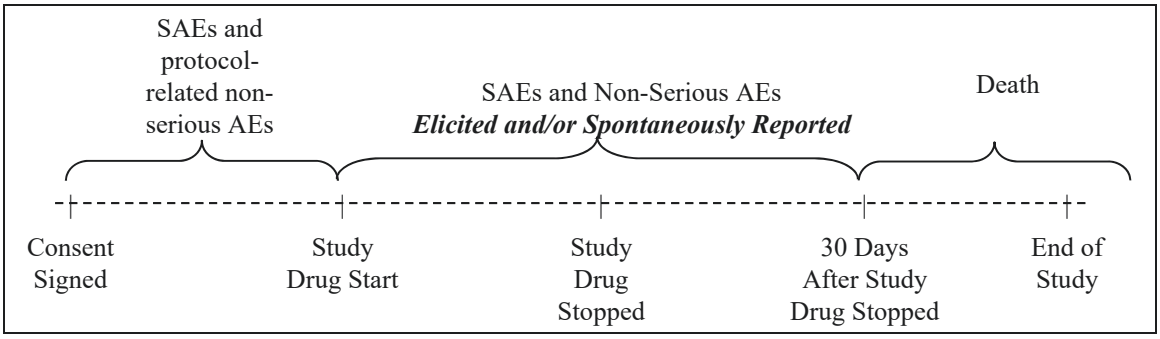
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for a serious adverse event.

6.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related non-serious 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. After Post-Treatment Week 4 until the end of the study, only SAE of death will be collected.

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. For SAEs that occur prior to the site having access to the RAVE® system or if RAVE is not operable, the forms should be faxed or emailed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

FAX to: +1 (847)-938-0660
Email: PPDINDPharmacovigilance@AbbVie.com

For safety concerns, contact the Antiviral Safety Team at:

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

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

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

Primary Study Designated Physician:

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

Telephone Contact Information:
Office:
Mobile:
Fax:
Email:

If the Primary Study Designated Physician is unavailable, the following Emergency Medical Service may be contacted:

Emergency Medical Service
Phone: +1 (973) 784-6402

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 6 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 who report a positive pregnancy test during the Treatment Period must be notified to stop RBV (if applicable) immediately. Administration of DAAs may be continued at the investigator's discretion after discussion

with the subject, if the benefit of continuing therapy is felt to outweigh the potential 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 6 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 the Sponsor 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 Sections 6.7.1 through 6.7.5.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the investigator or the Sponsor as having a "reasonable possibility" of being related to the study 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 satisfactory resolution.

Investigators should avoid interrupting study drugs for more than 7 consecutive days. The Investigator should ensure that any study drug interruptions or RBV (if applicable) 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 Grade 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) for subjects receiving RBV, Section 6.7.5 (Management of ALT Elevations), and Section 6.7.6 (Creatinine Clearance) may continue study drugs with follow-up per study protocol and in accordance with local standard of care.

6.7.2 Grade 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 the event 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 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 RBV experiences a hemoglobin decrease meeting one of the criteria outlined in Table 12, a confirmatory test should be performed. If the hemoglobin decrease is confirmed, the management guidelines in Table 12 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 12 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 outlined in Table 12.

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 12. Ribavirin Dose Modification Guidelines in Management of Hemoglobin Decreases

Hemoglobin Value	Intervention
Subjects with creatinine clearance ≥ 50 mL/min	
< 10 g/dL 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 hemoglobin increases to ≥ 12 g/dL, RBV may be restarted.
For subjects with creatinine clearance < 50 mL/min	
< 10 g/dL	Interrupt RBV. Manage the subject as medically appropriate. If hemoglobin increases to ≥ 10 g/dL, RBV may be restarted. If creatinine clearance increases to ≥ 50 mL/min, refer to guidance above.

* 1st dose reduction of ribavirin is by 200 mg/day. If needed, 2nd 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 tablet in the morning and two 200 mg tablets in the evening.

6.7.5 Management of ALT Elevations

Transient asymptomatic grades 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 the

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 ≥ 50 mL/min), or to below 30 mL/minute (in a subject with a 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 13. 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 needed. 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 13. 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

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

Clinical Toxicity Table will be appended to protocol in Appendix C.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review

Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitors:

Primary Contact:	Alternate Contact:
[redacted]	[redacted]
1 North Waukegan Road	1 North Waukegan Road
[redacted]	[redacted]
North Chicago, IL 60064	North Chicago, IL 60064
Office: [redacted]	Office: [redacted]
Fax:	Fax:

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.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will occur after all subjects have completed the study to evaluate the effect of response to treatment on clinical outcomes. An interim analysis will occur after all subjects have completed the Post-Treatment Week 12 Visit or prematurely discontinued from study to assess the percentage of subjects achieving SVR_{12}. For both primary and interim analyses, the data will be locked after performing appropriate data cleaning. Data after Post-Treatment Week 12 will be added to a subsequent version of the database. SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. All statistical tests and all confidence intervals will be two-sided with an α level of 0.05.

The intent-to-treat (ITT) population will consist of all enrolled subjects in this study (ITT-II) and companion study TOPAZ-I (ITT-I) who receive at least one dose of study

drug. The primary efficacy analysis on clinical outcomes will be performed on all subjects in the ITT population.

The ITT-II population will consist of all subjects enrolled in this study only who receive at least one dose of study drug. All other efficacy, safety, resistance and demographic analyses will be performed on all subjects in the ITT-II population.

No data will be imputed for any efficacy or safety analyses except for the PRO questionnaires and for analyses of the HCV RNA endpoints. If a respondent answers at least 50% of the items in a multi-item scale of the SF-36v2, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. Similarly, the missing items of the FACIT–F questionnaire will be imputed with the average score of the answered items in the same scale as long as more than 50% of the items in the scale were answered. The SF-36v2 Mental and Physical Component Summary measures will not be computed if any domain is missing.

HCV RNA values will be selected for the SVR_{12} analysis based on the 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-baseline 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. In addition, if a subject has an unquantifiable HCV RNA level at the preceding value and an undetectable HCV RNA level at the succeeding value, or vice versa, the HCV RNA level will be imputed as unquantifiable at this visit for this subject. Subsequent to this flanking 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). 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.

8.1.1 Demographics

Demographics and baseline characteristics will be summarized for all subjects in the ITT population. Demographics include age, weight, height, and BMI, and the frequency of gender, race and ethnicity. Baseline characteristics will include HCV genotype 1 subtype (1a, 1b, other), IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), treatment history (treatment-naïve [IFN-eligible, IFN-ineligible] or IFN/RBV treatment-experienced [null responder, partial responder, relapser, prior relapse/breakthrough, prior nonresponder, IFN-intolerant]), baseline HCV RNA levels [(continuous) and (≤ 800,000 IU/mL or > 800,000 IU/mL)], baseline HOMA-IR (< 3 mU × mmol/L^2 or ≥ 3 mU × mmol/L^2), baseline fibrosis stage (F0-1, F2, F3, F4), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status. Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI) and the number and percentage of subjects will be presented for categorical variables (e.g., gender and race).

8.1.2 Efficacy

The primary efficacy analysis on clinical outcomes will be performed on all subjects in the ITT population. All other efficacy analyses will be performed on the ITT-II population.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the COBAS® AmpliPrep HCV assay version 2.0. For this assay, the lower limit of quantification (LLOQ) is 15 IU/mL.

Incidence of all-cause death, liver-related death, liver decompensation, liver transplantation, and hepatocellular carcinoma as defined in protocol Section 5.3.1.1 will be collected during the 5-year (PT Week 260) Post-Treatment Period.

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is to assess the effect of response to treatment on clinical outcomes by comparing the time to incidence of the following events between subjects who achieve SVR_{12} and those who do not using a Cox regression model:

- All-cause death
- Liver-related death
- Liver decompensation
- Liver transplantation
- Hepatocellular carcinoma
- Composite of any of the above outcomes

The primary analysis will be conducted among subjects in the ITT population as described in Section 8.1.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

1. The percentage of subjects achieving SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The simple percentage of subjects achieving SVR_{12} will be calculated and a two-sided 95% confidence interval of the percentage will be computed using the Wilson score method for the binomial proportion.
2. The mean change from baseline in quality of life and fatigue to Post-Treatment Week 12 and to the Post-Treatment Week 24 (assessed by Short-Form 36 Version 2 health survey [SF-36v2] and the Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT–F] questionnaires) will be assessed by subjects' fibrosis stage at baseline.

Summary statistics (n, mean, SD, minimum and maximum) at Baseline and each applicable visit will be provided. In particular, the comparison of the mean change from baseline to Post-Treatment Week 12 and to Post-Treatment Week 24 in the SF-36v2 Vitality domain score, SF-36v2 Mental Component Summary Score and Physical Component Summary score and in the FACIT–F score among subjects who had different fibrosis stage at baseline will be performed using ANCOVA analyses with baseline fibrosis stage (F0-F1, F2, F3 and F4) as factor and baseline PRO score and SVR_{12} status as covariates.

3. Adherence to each tablet type (ABT-450/r/ABT-267, ABT-333, and RBV) during the Treatment Period will be calculated as the percentage of tablets taken relative to the total tablets expected to be taken for each tablet type.

8.1.2.3 Subgroup Analyses

Subgroup efficacy analyses on the clinical outcomes and the percentage of subjects achieving SVR_{12} will be performed as appropriate and useful.

8.1.2.4 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized and analyzed:

- The number and percentage of subjects meeting each and any of the following SVR_{12} non-response category:
  - On-treatment virologic failure (rebound or fail to suppress)
  - Relapse
  - Premature study drug discontinuation with no on-treatment virologic failure
  - Missing SVR_{12} data
  - Other
- Additional analysis on the PRO data will be performed as useful and appropriate.

8.1.3 Resistance

For subjects who do not achieve or maintain SVR_{12} and who are included in the analyses described below, the sample closest in time after virologic failure with an HCV RNA level ≥ 1000 IU/mL will be used if the HCV RNA level at the time of failure is < 1000 IU/mL. The prototypic reference strains with their associated GenBank Accession IDs for sequence analyses are genotype 1a-H77 (NC_004102) and 1b-Con1 (AJ238799).

For each DAA target, resistance-associated signature amino acid variants will be identified by AbbVie Clinical Virology. Amino acid positions where resistance-associated variants have been identified in vitro and/or in vivo are 1) for ABT-450: 36, 43, 56, 155, 156, and 168 in NS3 for genotype 1a; 56, 155, 156, and 168 in NS3 for genotype 1b; 2) for ABT-267: 28, 30, 31, 32, 58, and 93 in NS5A for genotype 1a; 28, 29, 30, 31, 32, 58, and 93 in NS5A for genotype 1b; and 3) for ABT-333: 316, 414, 446, 448, 451, 553, 554, 555, 556, 558, 559, and 561 in NS5B for genotype 1a; 316, 368, 411, 414, 445, 448, 553, 556, 558, and 559 in NS5B for genotype 1b.

The following definitions will be used in the resistance analyses:

- Baseline sample: sample collected before the first dose of DAA study drug.
- Baseline variant: a variant in the 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 (NS3, NS5A, or NS5B).
- Post-baseline variant: an amino acid variant in a post-baseline time point sample that was not detected at baseline.
- Linked variant by population sequencing: variants at 2 or more signature resistance-associated amino acid positions identified within a target by population sequencing, and no mixture of amino acids is detected at any of these positions.

For those samples evaluated, a listing by subject of all baseline variants relative to prototypic reference sequence at signature resistance-associated amino acid positions will be provided for each DAA target (NS3, NS5A, and/or 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 subtype out of the total number of baseline samples sequenced will also be provided.

The HCV amino acid sequence at post-baseline time points with an HCV RNA level of ≥ 1000 IU/mL that are analyzed will be compared to the baseline and appropriate prototypic reference amino acid sequences. Listing by subject and time point of all post-baseline variants at signature resistance-associated amino acid positions relative to the baseline and to the appropriate prototypic reference amino acid sequences will be provided.

Linkage between variants at signature resistance-associated amino acid positions by population sequencing will also be evaluated. A listing by subject and time point of the linked variants by population sequencing will be provided. In addition, a summary of the number and percentage of subjects with linked variants within each target by HCV subtype out of the total number of baseline samples sequenced will be provided.

The persistence of resistance-associated substitutions that emerged for each target (NS3, NS5A, and NS5B) will be assessed by population sequencing at selected post-treatment time points in a subset of subjects. Listings by subject and time point of all post-baseline variants at signature resistance-associated amino acid positions relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B).

8.1.4 Safety

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

8.1.4.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent adverse events by severity 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.

8.1.4.2 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.

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.

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. Additional analyses will be performed if useful and appropriate.

8.1.4.3 Vital Signs Data

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each Post-Baseline Visit will be summarized descriptively. Number and percentages of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant vital signs values during treatment will be summarized.

8.2 Determination of Sample Size

Assuming 4% of subjects do not achieve SVR_{12} and assuming the 5-year composite event rate of all clinical outcomes is 20% in non-SVR_{12} subjects and 75% of reduction in SVR_{12} subjects (Hazard Ratio of 0.25),[16,17] then based on two sample log rank test in EAST 6.0, a sample size of at least 2,000 subjects overall enrolled in the TOPAZ-I and TOPAZ-II studies provides greater than 80% power to reject the null hypothesis of no difference between SVR_{12} and non-SVR_{12} subjects in the rate of clinical outcome events. Power calculations were based on a dropout rate of up to 20%.

8.3 Randomization Methods

This is a single arm, open-label study. Therefore, there is no randomization in this study. Enrolled subjects will receive treatment per the planned study schematic outlined in Section 5.1. Enrolled subjects will also receive a Care Plan based on the level assessment as described in Section 5.3.1.1. The Care Plan level may be adjusted as needed throughout the trial until subjects have completed their Post-Treatment Week 12 visit.

9.0 Ethics

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

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

ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

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

documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If a subject continues on DAA after becoming pregnant during the treatment, the subject should sign the informed consent approved by their IRB. 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.

Informed consent should also be obtained if a subject discontinues early from the study and agrees to be contacted over the telephone at each scheduled yearly visit to collect the survival status. 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.

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, subject portal, 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. Any data recorded directly on the web-based care model [(if applicable) i.e., no prior written or electronic data] will be considered as source data.

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 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.

13.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for ABT-450, ABT-267, ABT-333 and the product labeling for RBV
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	An Open-Label, Multicenter Study to Evaluate Long-term Outcomes with ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (TOPAZ II)
Protocol Date:	19 December 2014

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 13.0 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]		Statistics
		Clinical
		Clinical
		Global Drug Supply Management
		Clinical

Appendix C. Clinical Toxicity Grades

Clinical Toxicity Grades for HCV Studies[1,2]

	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
HEMATOLOGY				
ABSOLUTE NEUTROPHIL COUNT DECREASED	<LLN – 1500/mm3 <LLN – 1.5 × 10e9/L	<1500 – 1000/mm3 <1.5 – 1.0 × 10e9/L	<1000 – 500/mm3 <1.0 – 0.5 × 10e9/L	<500/mm3 <0.5 × 10e9/L
EOSINOPHIL COUNT INCREASED	650-1500 cells/mm3	1501-5000 cells/mm3	>5000 cells/mm3	Hypereosinophilic
HEMOGLOBIN DECREASED	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L
INTERNATIONAL NORMALIZED RATIO (INR), INCREASED	>1 – 1.5 × ULN	>1.5 – 2 × ULN	>2 × ULN	
LYMPHOCYTE COUNT DECREASED	<LLN – 800/mm3 <LLN × 0.8 – 10e9/L	<800 – 500/mm3 <0.8 – 0.5 × 10e9/L	<500 – 200 mm3 <0.5 – 0.2 × 10e9/L	<200/mm3 <0.2 × 10e9/L
PLATELETS DECREASED	<LLN – 75,000/mm3 <LLN – 75.0 x 109 /L	<75,000-50,000/mm3 <75.0 – 50.0 x 109 /L	<50,000-25,000/mm3 <50.0 – 25.0 x 109 /L	<25,000/mm3 <25.0 x 109 /L
PTT	>1 – 1.5 × ULN	>1.5 – 2 × ULN	>2 × ULN	
WHITE BLOOD CELL COUNT DECREASED	<LLN – 3000/mm3 <LLN – 3.0 × 10e9/L	<3000 – 2000/mm3 <3.0 – 2.0 × 10e9/L	<2000 – 1000/mm3 <2.0 – 1.0 × 10e9/	<1000/mm3 <1.0 × 10e9/L
WHITE BLOOD CELL COUNT INCREASED	10,800 – 15,000 cells/mm3	>15,000 – 20,000 cells/mm3	>20,000 – 25,000 cells/mm3	>25,000 cells/mm3
CHEMISTRIES				
ALBUMIN, SERUM, LOW	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	
BILIRUBIN, HIGH	>ULN – 1.5 × ULN	>1.5 – 3.0 × ULN	>3.0 – 10.0 × ULN	>10.0 × ULN
BUN	1.25-2.5 × ULN	>2.5 -5.0 × ULN	>5 -10.0 × ULN	>10 × ULN
CALCIUM, SERUM LOW	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
CALCIUM, SERUM HIGH	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
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; 08 June 2009

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

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

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

Appendix D. Protocol Amendment : List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.2 Synopsis
Subsection Secondary Objectives:
Last bullet previously read:

- To evaluate adherence to study drug regimens with the Subject Care Plan Model.

Has been changed to read:

- Adherence to the prescribed regimen (measured by pill counts for each type of tablet).

Section 1.2 Synopsis
Subsection Methodology:
Second paragraph, third sentence previously read:

At least 50, but no more than 100 subjects with fibrosis stage of F3 will be allowed to enroll.

Has been changed to read:

At least 50, but no more than 110 subjects with fibrosis stage of F3 will be allowed to enroll.

Section 1.2 Synopsis
Subsection Methodology:
Tenth paragraph, last sentence previously read:

The treatment duration will be 12 weeks for all subjects except HCV GT1a infected prior IFN/RBV null responder and IFN/RBV nonresponder subjects with compensated cirrhosis who will receive treatment for 24 weeks.

Has been changed to read:

The treatment duration will be 12 weeks for all subjects except HCV GT1a infected subjects with compensated cirrhosis, who will receive treatment for 24 weeks unless a treatment duration of 12 weeks is selected by the investigator based on the subject's prior treatment history.

Section 1.2 Synopsis
Subsection Methodology:
Add: new eleventh paragraph

HCV GT1a-infected subjects with compensated cirrhosis who were assigned to 12 weeks of treatment under a previous version of this protocol will be assigned to 12 additional weeks of treatment unless 1) the investigator determines that a 12-week duration of therapy is appropriate based on the subject's prior treatment history; or 2) the subject has already completed the original study drug treatment and additional treatment cannot be initiated within 15 days of the date that the original 12-week treatment was completed.

Section 3.2 Benefits and Risks
Second paragraph, last sentence previously read:

For this reason, HCV GT1a-infected subjects with compensated cirrhosis and who were prior null responders to IFN/RBV will receive 3-DAA with RBV for 24 weeks.

Has been changed to read:

For this reason, in previous versions of the protocol, HCV GT1a-infected subjects with compensated cirrhosis and who were prior null responders to IFN/RBV were assigned to receive 3-DAA with RBV for 24 weeks, while HCV GT1a-infected subjects with compensated cirrhosis who were not prior null responders to IFN/RBV were assigned to received 3-DAA with RBV for 12 weeks. In order to align the treatment duration for subjects with GT1a infection and compensated cirrhosis with the recommended treatment duration that is found in the US prescribing information for the recently-approved AbbVie product containing the regimen included in this study (i.e., ABT-450/r/ABT-267 and ABT-333), the protocol now specifies that all HCV GT1a-infected subjects with

compensated cirrhosis will be assigned to receive 3-DAA with RBV for 24 weeks, unless a treatment duration of 12 weeks is selected by the investigator based on the subject's prior treatment history. HCV GT1a-infected subjects with compensated cirrhosis who were assigned to 12 weeks of treatment under a previous version of this protocol will be assigned to 12 additional weeks of treatment unless 1) the investigator determines that a 12-week duration of therapy is appropriate based on the subject's prior treatment history; or 2) the subject has already completed the original study drug treatment and additional treatment cannot be initiated within 15 days of the date that the original treatment was completed.

Section 4.0 Study Objectives
Subsection <u>Secondary Objectives:</u>
Last bullet previously read:

- To evaluate adherence to study drug regimens with the Subject Care Plan Model.

Has been changed to read:

- Adherence to the prescribed regimen (measured by pill counts for each type of tablet).

Section 5.1 Overall Study Design and Plan: Description
Tenth paragraph, second sentence previously read:

At least 50, but no more than 100 subjects with fibrosis stage of F3 will be allowed to enroll.

Has been changed to read:

At least 50, but no more than 110 subjects with fibrosis stage of F3 will be allowed to enroll.

Section 5.1.2 Treatment Period (TP)
Second paragraph, third sentence previously read:

The treatment duration will be 12 weeks for all subjects except HCV GT1a-infected prior IFN/RBV null responder and IFN/RBV nonresponders subjects with compensated cirrhosis who will receive treatment for 24 weeks.

Has been changed to read:

The treatment duration will be 12 weeks for all subjects except HCV GT1a-infected subjects with compensated cirrhosis, who will receive treatment for 24 weeks unless a treatment duration of 12 weeks is selected by the investigator based on the subject's prior treatment history.

Table 5. Study Drug Regimen
Previously read:

Subject		Treatment Regimen	Treatment Duration
HCV GT1a-infected subjects*	without cirrhosis	ABT-450/r/ABT-267 + ABT-333 + RBV	12 weeks
	with compensated cirrhosis who are: • treatment-naïve • prior IFN/RBV partial responder • prior IFN/RBV relapser • prior IFN/RBV relapse/breakthrough • IFN intolerant		
	with compensated cirrhosis who are: • prior IFN/RBV null responders • prior IFN/RBV nonresponder	ABT-450/r/ABT-267 + ABT-333 + RBV	24 weeks
HCV GT1b-infected subjects	without cirrhosis	ABT-450/r/ABT-267 + ABT-333	12 weeks
	with compensated cirrhosis	ABT-450/r/ABT-267 + ABT-333 + RBV	12 weeks

* Includes subjects that are unable to be subtyped.

Has been changed to read:

Subject Population	Treatment Regimen*	Treatment Duration
Genotype 1a, without cirrhosis	ABT-450/r/ABT-267 + ABT-333 + ribavirin	12 weeks
Genotype 1a, with cirrhosis	ABT-450/r/ABT-267 + ABT-333 + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	ABT-450/r/ABT-267 + ABT-333	12 weeks
Genotype 1b, with cirrhosis	ABT-450/r/ABT-267 + ABT-333 + ribavirin	12 weeks

* Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

** Treatment for 12 weeks may be considered for some patients based on prior treatment history *(See response rates in GT1a cirrhotics by prior treatment history protocol Section 3.0, Table 1)*.

Section 5.1.2 Treatment Period (TP)
Third paragraph previously read:

The site will enter subject's genotype (1b / Non-1b), fibrosis stage and prior IFN/RBV null responders and nonresponder information in the IRT system in order to assign subject's treatment regimen as described in Table 5.

Has been changed to read:

The site will enter subject's genotype (1b / Non-1b), fibrosis stage and prior IFN/RBV null responders and nonresponder information in the IRT system (Table 5).

Section 5.3.1.1 Study Procedures
Subsection Subject Care Plan Model
Add: new second sentence to third paragraph

However, if the web-based portal is not operable, or the site information is not available in the portal, the nurse educator may obtain this information verbally from the site.

Section 5.3.1.1 Study Procedures
Subsection Subject Care Plan Model
Delete: third sentence from fifth paragraph

Subjects who successfully complete the initial assessment with the nurse educator will receive an email to set-up their profile in the portal and they will have approximately 7 days to complete this task.

Section 5.3.1.1 Study Procedures
Subsection Subject Care Plan Model
Heading "Subject Care Plan Levels:"
Fourth paragraph, second, third and last sentence previously read:

The site will enter subjects' scheduled visit dates, actual visit dates, concomitant medication, and treatment duration into the web-based portal. Additionally, the investigative site personnel will utilize the portal to view and enter subject's current assigned care level into the EDC system. The subject may use the web-portal as a resource to confirm that they are taking their AM and PM doses (if needed, the site personnel or nurse educator may assist the subject with this activity).

Has been changed to read:

The site may enter subjects' scheduled visit dates, actual visit dates, concomitant medication, and treatment duration into the web-based portal. The nurse educators or site personnel may use the web-portal as a resource to confirm that the subject is taking their AM and PM doses.

Section 5.3.1.1 Study Procedures
Subsection Subject Care Plan Model
Heading "Subject Care Plan Levels:"
Delete: first sentence from fifth paragraph

Subjects may also be required to complete survey at approximately Week 6 (after Day 1 Study Visit) and complete study drug tracker as noted above.

Section 6.5 Adverse Event Reporting
Add: new last paragraph and "Emergency Medical Service" box

If the Primary Study Designated Physician is unavailable, the following Emergency Medical Service may be contacted:

Emergency Medical Service
Phone: +1 (973) 784-6402

Appendix B. List of Protocol Signatories
Previously read:

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

Has been changed to read:

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