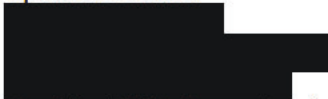
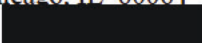


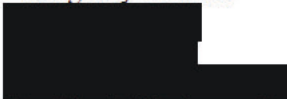
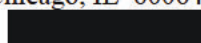




## 1.0 Title Page

### Clinical Study Protocol M14-423

# 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-I)

## Incorporating Amendments 1 and 2

AbbVie Investigational Product:	ABT-450/r/ABT-267, ABT-333, RBV	
Date:	19 January 2015	
Development Phase:	3b	
Study Design:	Open-label combination drug study	
EudraCT Number:	2014-001022-14	
Investigator:	Multicenter. Investigator information is on file at AbbVie.	
Sponsor:	AbbVie*	
Sponsor/Emergency Contact:	<b>Sponsor Contact:</b>  One North Waukegan Road North Chicago, IL 60064 Phone:  Fax:  Mobile:  Central Back-Up Phone: +1 (973) 784-6402	<b>Emergency Contact:</b>  One North Waukegan Road North Chicago, IL 60064 Phone:  Fax:  Mobile: 

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

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

**Confidential Information**

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

## 1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Update the treatment duration for subjects with GT1a infection and compensated cirrhosis (F4 fibrosis stage) from 12 to 24 weeks, with 12 weeks considered for some patients where consistent with the local label.

*Rationale: To align the treatment duration for these subjects with that recommended in the prescribing information of section of the approved local product labels in countries where the AbbVie product containing the regimen for this study (i.e., ABT-450/r/ABT-267 and ABT-333) has received marketing authorization.*

- Update Introduction to remove language detailing effects of ABT-450/ritonavir, ABT-267 (and its major, inactive human metabolites) and ABT-333 on embryo-fetal development.

*Rationale: Results of embryo-fetal toxicity studies are described in the locally approved labels and in the investigator brochures.*

- Update Introduction to refer investigators to locally approved labels for preclinical toxicology (including reproductive and development toxicity), metabolism, pharmacokinetics and drug-drug interactions in countries that have received marketing approval.
- Clarify elevated ALT risk associated with ethinyl estradiol therapy in Section 3.0 Introduction; Integrated Safety Results.

*Rationale: AbbVie re-evaluated data on grade 3 or higher post-baseline serum ALT values in subjects and identified concurrent use of ethinyl estradiol as a risk factor for ALT elevations. Concurrent use of estrogens other than ethinyl estradiol was not associated with an increased risk of grade 3+ ALT values, and therefore, there are no contraindications for these estrogen products that are commonly used in hormone replacement.*

- Clarify enrollment caps for cirrhotic subjects.
- Update Contraindicated Medication list in Synopsis and Exclusion 3 (Table 6) to refer investigators to locally approved labels where AbbVie product containing the regimen for this study has been approved.

*Rationale: To align the contraindicated medication list with that recommended in the prescribing information section of the approved local product labels in countries where the AbbVie product containing the regimen for this study has received marketing authorization.*

- Update Schedule of Activities ([Table 7](#)) removing duplicate "Study Drug Returned for IRT Reconciliation" entry.
- Update Schedule of Activities ([Table 7](#), footnote "j.") and Section 5.3.1.1 to clarify urine pregnancy testing requirements for subjects on DAA regimen only.
- Add AFP to the list of Clinical Laboratory Tests collected at the Screening Visit.

*Rationale: To more fully characterize the subject's baseline laboratory status.*

- Update [Table 12](#) to allow for RBV dose modifications in management of hemoglobin decreases per local label.
- Update Section 9.1 to include submission of amendments to Regulatory Authority(ies) as applicable.
- Update [Table 4](#) (Baseline Fibrosis Stage) to correct administrative error for F4 FibroScan range.
- Add back-up Sponsor contact phone number to Title Page and Section 6.5.

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

## 1.2 Synopsis

<b>AbbVie Inc.</b>	<b>Protocol Number:</b> M14-423
<b>Name of Study Drug:</b> ABT-450, ritonavir, ABT-267 and ABT-333 with or without ribavirin (RBV)	<b>Phase of Development:</b> 3b
<b>Name of Active Ingredient:</b> ABT-450 Ritonavir ABT-267 ABT-333 Ribavirin	<b>Date of Protocol Synopsis:</b> 19 January 2015
<b>Protocol Title:</b> 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-I)	
<b>Objectives:</b> The primary objective of this study is to evaluate the effect of response to treatment (assessed by SVR <sub>12</sub> 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. <b>Secondary Objectives:</b> <ul style="list-style-type: none"> <li>To evaluate the long-term progression of fibrosis by baseline fibrosis stage and sustained virologic response, as measured by change from baseline in liver stiffness measured by transient elastography (FibroScan<sup>®</sup>) when available, in adults with genotype 1 (GT1) chronic HCV infection who received treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin.</li> <li>To evaluate the percentage of subjects achieving SVR<sub>12</sub> with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin in adults with GT1 chronic HCV infection.</li> </ul>	
<b>Investigators:</b> Multicenter, investigator information on file at AbbVie	
<b>Study Sites:</b> Approximately 200 sites	
<b>Study Population:</b> Adults at least 18 years of age, with GT1 chronic HCV infection, with or without compensated cirrhosis, who are treatment-naïve or IFN-based therapy treatment-experienced.	
<b>Number of Subjects to be Enrolled:</b> Approximately 1650 subjects	

**Methodology:**

The TOPAZ studies are composed of 2 studies (TOPAZ-I [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-I) is a Phase 3b, open-label, multi-center study designed together with companion study TOPAZ-II, which shares the primary objective of evaluating the effect of SVR<sub>12</sub> 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-based therapy (IFN or pegIFN monotherapy, IFN/RBV, or pegIFN/RBV) treatment-experienced. In both studies, subjects will be treated with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin (RBV).

Subjects meeting the eligibility criteria will be enrolled until approximately 1650 subjects have been enrolled at approximately 200 sites.

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 IFN-based therapy treatment experienced 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; these subjects will receive treatment for 24 weeks. Treatment duration of 12 weeks for HCV GT1a-infected subjects with compensated cirrhosis may be selected by the investigator where consistent with the local approved label, in countries where marketing authorization has been granted for the regimen included in this study.

HCV GT1a-infected subjects with compensated cirrhosis who were originally assigned to 12 weeks of treatment under a previous version of this protocol will be assigned to 24 weeks of treatment unless 1) the investigator determines that a 12-week duration of therapy is appropriate based on the approved local label; 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.

Post-Treatment Period: subjects who receive at least one dose of study drug will be followed for up to 260 weeks. At these visits subjects will be assessed for antiviral response, progression of liver fibrosis, and clinical outcomes, including all-cause death, liver-related death, occurrence of hepatocellular carcinoma, liver decompensation and liver transplantation.

The number of cirrhotic subjects (an equivalent Metavir score of F4) will be limited to less than or approximately equal to 400 subjects; the number of subjects enrolled without fibrosis or with portal fibrosis without septa (an equivalent Metavir score of F0 or F1 respectively) will be limited to 1000 subjects. In the absence of a qualifying liver biopsy, the equivalent Metavir score corresponding to the results of a screening FibroScan or FibroTest will be used to determine the fibrosis stage.

**Diagnosis and Main Criteria for Inclusion/Exclusion:**

**Main Inclusion:**

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 7 months after stopping study drug if receiving RBV (or as directed by local RBV label). (Note: Ethinyl estradiol-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 7 months after stopping study drug if receiving RBV (or as directed by local RBV label).
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.

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

**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 whichever is longer, prior to study drug administration including but not limited to:

For additional medications contraindicated with AbbVie's 3 DAA regimen, refer to the recommended prescribing information section of the approved local product labels in countries where the regimen contained in this study (i.e., ABT-450/r/ABT-267 and ABT-333) has received marketing authorization. If locally approved labels are not available, refer to the following Contraindicated Medication list:

Alfuzosin	Ethinyl estradiol-containing medications	Pimozide
Astemizole	Fusidic Acid	Rifampin
Carbamazepine	Gemfibrozil	Salmeterol
Cisapride	Lovastatin	Sildenafil*
Dihydroergotamine	Methylergonovine	Simvastatin
Efavirenz	Midazolam (oral)	St. John's Wort
Ergotamine	Phenobarbital	Terfenadine
Ergonovine	Phenytoin	Triazolam

\* When used for the treatment of pulmonary arterial hypertension.

Note: Not all medications contraindicated with ritonavir, ribavirin, and 3DAA regimen are listed above. Refer to the most current package inserts or product labeling of ritonavir and ribavirin for a complete list of contraindicated medications.

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:  

$$\text{CrCl} = [(140 - \text{Age}) \times \text{Mass (in kg)} \times (0.85 \text{ if female})] / [72 \times \text{Serum creatinine (in mg/dL)}]$$
  - Albumin < 2.8 g/dL
  - Hemoglobin < LLN
  - Platelets < 25,000 cells per mm<sup>3</sup>
  - 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/r/ABT-267: 75 mg/50 mg/12.5 mg tablet  
 ABT-333: 250 mg tablet  
 Ribavirin: 200 mg tablet



<b>Doses:</b>	ABT-450/r/ABT-267: 150/100/25 mg QD ABT-333: 250 mg BID Ribavirin: weight-based dosing 1000 or 1200 mg divided twice daily or adjusted for renal impairment subjects
<b>Mode of Administration:</b>	Oral
<b>Reference Therapy:</b>	Not applicable
<b>Dose:</b>	Not applicable
<b>Mode of Administration:</b>	Not applicable
<b>Duration of Treatment:</b>	Subjects will receive ABT-450/r/ABT-267 and ABT-333 with or without RBV for 12 or 24 weeks.
<b>Criteria for Evaluation:</b>	<p><b>Efficacy:</b> 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.</p> <p><b>Patient Reported Outcomes (PROs):</b> During treatment and post-treatment, fatigue and general health related quality of life will be assessed using the short form 36 version 2 (SF-36v2) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT–F) questionnaires.</p> <p><b>Safety:</b> Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests and vital signs.</p>
<b>Statistical Methods:</b>	<p><b>Efficacy:</b> Primary efficacy endpoint is the effect of response to treatment (assessed by SVR<sub>12</sub>) on clinical outcomes, based on subjects in this study and companion study TOPAZ II. The endpoint will be assessed by comparing the incidence of the following events between subjects who achieve SVR<sub>12</sub> and those who do not using the Cox regression model:</p> <ul style="list-style-type: none"> <li>• All-cause death</li> <li>• Liver-related death</li> <li>• Liver decompensation</li> <li>• Liver transplantation</li> <li>• Hepatocellular carcinoma</li> <li>• Composite of any of the above outcomes</li> </ul> <p>Secondary endpoint analyses:</p> <ul style="list-style-type: none"> <li>• The long-term change from baseline in liver stiffness (as assessed by transient elastography [Fibroscan<sup>®</sup>]), when available, will be assessed by baseline fibrosis stage and sustained virologic response.</li> <li>• The percentage of subjects achieving SVR<sub>12</sub> and 2-sided 95% confidence interval will be presented by baseline fibrosis score (F0-F1, F2, F3 and F4).</li> </ul>



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**Statistical Methods (Continued):****Resistance:**

The following resistance information will be provided for a subset of the subjects who experience virologic failure: 1) the amino acid variants at signature resistance-associated positions at baseline 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.

**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. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA preferred term) is presented by severity (mild, moderate, or severe) and relationship to study drugs.

Change from baseline in laboratory tests and vital sign measurements to each time point of collection will be summarized. 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.

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### 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
AFP	Alpha-fetoprotein
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
CrCl	Creatinine Clearance
CRF	Case report form
CYP2C8	Cytochrome P450 2C8
CYP3A	Cytochrome P450 3A
DAA	Direct-acting antiviral agent
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
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
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus

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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
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NS3	Nonstructural viral protein 3A
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
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

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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 <sub>12</sub>	Sustained virologic response 12 weeks post-treatment
ULN	Upper limit of normal
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

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### 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.<sup>1</sup> Cirrhosis develops after prolonged HCV infection.<sup>2</sup> 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.<sup>3-6</sup> Without liver transplantation, decompensated cirrhosis leads to death in 50% to 72% of patients after 5 years.<sup>7</sup> 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.<sup>8</sup>

Treatment of HCV-infected patients could reduce the risk of cirrhosis, decompensation, cancer and liver-related deaths. Among patients treated with pegylated interferon (pegIFN) and ribavirin (RBV) 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).<sup>9</sup> 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).<sup>10</sup> Patients with SVR following treatment with pegIFN with or without RBV have also shown improvement in liver histology and a reduction in liver-related death in several studies.<sup>11-13</sup> 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.<sup>14-16</sup> In patients with advanced fibrosis and cirrhosis, viral suppression by more than 4 logs<sub>10</sub> with pegIFN and RBV was associated with marked reduction in death/liver transplantation, and in liver-related morbidity and death.<sup>17</sup>

In patients with HCV infection, liver histology is a key determinant of clinical complications such as decompensation and hepatocellular carcinoma as the risk is greatest in patients with advanced fibrosis. Treatment with IFN-based therapy with or without RBV has demonstrated a delay in fibrosis progression in patients who relapse and regression of fibrosis in patients with SVR. While liver biopsy remains the reference standard, noninvasive tests such as transient elastography (FibroScan) have emerged as validated methods to evaluate degree of liver fibrosis and to monitor progression and regression of fibrosis.<sup>18</sup> Whereas liver stiffness increased or did not change over time in untreated patients, patients treated with pegIFN/RBV therapy exhibited decreases in liver stiffness during and after treatment with the greatest improvements observed in patients with more advanced fibrosis at baseline.<sup>19-21</sup>

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](#).

**Table 1. Pooled SVR<sub>12</sub> 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	3-DAA + RBV 12 Weeks	3-DAA + RBV 24 Weeks
	SVR <sub>12</sub>	SVR <sub>12</sub>	SVR <sub>12</sub>
Genotype 1b non-cirrhotics			
Naïve	99.0	98.9	--
Null	100	94.4	--
Partial	100	98.1	--
Relapser	100	98.5	--
Genotype 1a non-cirrhotics			
Naïve	90.2	95.7	--
Null	--	95.4	--
Partial	--	100	--
Relapser	--	94.0	--
Genotype 1b cirrhotics			
Naïve	--	100	100
Null	--	100	100
Partial	--	85.7*	100
Relapser	--	100	100
Genotype 1a cirrhotics			
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<sub>12</sub> 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<sub>12</sub> 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. Studies M13-961 and M14-002 are ribavirin 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, Study 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<sub>12</sub> rates were 96.6% in the 3-DAA + RBV arm and 100% in the 3-DAA without RBV arm. The difference in SVR<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> rates was driven largely by a lower SVR<sub>12</sub> 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-Week 3-DAA + RBV	12-Week PBO	12-Week 3-DAA + RBV	12-Week 3-DAA	12-Week 3-DAA + RBV	24-Week 3-DAA + RBV
Events, %	N = 770	N = 255	N = 401	N = 509	N = 208	N = 172
Subjects $\geq$ 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 <sup>a</sup>	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  $\geq$  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  $\geq 10\%$  Frequency in at Least One Arm of the Analysis and Rates of Key Post-Baseline Lab Abnormalities**

	Placebo-Controlled		Regimen-Controlled		Cirrhotics	
	12-Week 3-DAA + RBV	12-Week PBO	12-Week 3-DAA + RBV	12-Week 3-DAA	12-Week 3-DAA + RBV	24-Week 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 $\times$ ULN (Gr 3)	1.2	3.9	0.7	0.2	2.9	0
Bilirubin						
> 3 $\times$ 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

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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  $\geq$  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 postbaseline serum ALT elevations of  $> 5 \times$  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 ethinyl estradiol-containing therapy (i.e., combination contraceptives) 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 ethinyl estradiol-containing medications is a risk factor for these postbaseline elevations in serum ALT. There was no increase in the risk of ALT elevations greater than  $5 \times$  ULN in subjects on estrogens other than ethinyl estradiol (i.e., estradiol, conjugated estrogens) or in subjects on only progestins. 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.

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 (including reproductive and development toxicity), metabolism, pharmacokinetics and drug-drug interactions can be found in the Investigator's Brochure for ABT-267, ABT-450, ABT-333 or prescribing information for ombitasvir/paritaprevir/r and dasabuvir in countries with marketing authorization, and product label for ritonavir and ribavirin.<sup>22-26</sup>

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 3-DAA regimen with or without RBV was explored in treatment-naïve and treatment-experienced HCV GT1-infected subjects with or without compensated cirrhosis, in several Phase 3 studies. These studies were conducted in a randomized, controlled, double-blind or open-label fashion. This study is a Phase 3b, single arm, open-label study in approximately 1650 treatment-naïve and IFN-based therapy treatment-experienced subjects.

This is the first study to evaluate long term outcomes with ABT-450/r/ABT-267 and ABT-333 with or without RBV for 12 or 24 weeks in subjects with chronic HCV GT1 infection outside of the US. The study population comprises HCV GT1 infected subjects who are treatment-naïve or treatment-experienced, including subjects with and without cirrhosis. The study will include up to 25% of subjects with compensated cirrhosis which approximates the projected prevalence among chronic HCV-infected subjects.<sup>27</sup>

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### 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 ABT-450/r/ABT-267 and ABT-333 with or without RBV have been evaluated in six Phase 3 studies. Treatment with ABT-450/r/ABT-267 and ABT-333 with RBV for 12 weeks resulted in SVR<sub>12</sub> 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<sub>12</sub> following treatment with ABT-450/r/ABT-267 and ABT-333, 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<sub>12</sub> following treatment with ABT-450/r/ABT-267 and ABT-333, 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<sub>12</sub> following treatment with and without RBV, respectively, suggesting that ABT-450/r/ABT-267 and ABT-333 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 cirrhotics 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<sub>12</sub> following treatment for 12 and 24 weeks, respectively. Analysis of subgroups demonstrated that the difference in SVR<sub>12</sub> rates between treatment arms was due to the lower SVR<sub>12</sub> 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, suggesting that the longer duration of 24 weeks is required only for HCV GT1a null responders. 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 this protocol HCV GT1a-infected subjects with compensated cirrhosis and who were prior null responders or non-responders to pegIFN/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 or non-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 prescribing information of some approved local labels for the 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. Treatment duration of 12 weeks for HCV GT1a-infected subjects with compensated cirrhosis may be selected by the investigator where consistent with the approved local label.

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 24 weeks of treatment unless 1) the investigator determines that a 12-week duration of therapy is appropriate based on the approved local label; 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 comparison is favorable.

## **4.0 Study Objectives**

### **Primary Objective**

The primary objective of this study is to evaluate the effect of response to treatment (assessed by SVR<sub>12</sub> 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 long-term progression of fibrosis by baseline fibrosis stage and sustained virologic response, as measured by change from baseline in liver stiffness measured by transient elastography (FibroScan<sup>®</sup>) when available, in adults with genotype 1 (GT1) chronic HCV infection who received treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin.
- To evaluate the percentage of subjects achieving SVR<sub>12</sub>, with ABT-450/r/ABT-267 and ABT-333 with or without RBV in adults with GT1 chronic HCV infection.

## **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-II (M14-222), 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-based therapy (IFN or pegIFN monotherapy, IFN/RBV or pegIFN/RBV) treatment-experienced. In both studies, subjects will be treated with ABT-450/r/ABT-267 and ABT-333 with or without RBV.

In the TOPAZ-I and TOPAZ-II studies, the primary objective is to assess the effect of treatment response (SVR<sub>12</sub>) 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 outside the US while the TOPAZ-II study will be conducted in the US) and based on certain procedures that are not related to the primary outcome. For example, this study will assess the long-term change from baseline in liver elastography, and the TOPAZ-II study will utilize a Subject Care Plan Model to facilitate subjects' adherence to the study drug.

The study is designed to enroll 1650 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.

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-based therapy excluding DAAs (including IFN or pegIFN monotherapy, IFN/RBV or pegIFN/RBV). Subjects with documentation required to classify prior response to IFN/RBV or pegIFN/RBV treatment will be categorized as one of the following:

- Prior IFN/RBV or pegIFN/RBV null-responder: failed to achieve a 1 log<sub>10</sub> IU/mL reduction in HCV RNA by Week 4 or a 2 log<sub>10</sub> IU/mL reduction in HCV RNA by Week 12 during a prior IFN/RBV or pegIFN/RBV treatment course;
- Prior IFN/RBV or pegIFN/RBV partial responder: achieved at least a 2 log<sub>10</sub> 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;

- Prior IFN/RBV or pegIFN/RBV 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-based treatment experience, including those subjects with incomplete HCV RNA and treatment date documentation, will be categorized as one of the following:

- Prior IFN/RBV or pegIFN/RBV relapse/breakthrough: achieved at least one documented result of HCV RNA undetectable during a prior IFN/RBV or pegIFN/RBV treatment course;
- Prior IFN/RBV or pegIFN/RBV 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;
- Interferon intolerant: did not meet any of the above definitions of treatment-failure and discontinued IFN/RBV or pegIFN/RBV therapy due to IFN intolerability.
- Interferon experienced-other: Includes IFN or pegIFN monotherapy, IFN/RBV, or pegIFN/RBV experienced subjects. Includes subjects who do not have adequate documentation of response.

Note: subjects receiving IFN or pegIFN monotherapy must be categorized as 'Interferon experienced-other'.

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  $\leq 0.72$  and Aspartate Aminotransferase to Platelet Ratio Index (APRI)  $\leq 2$ .

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  $\geq 14.6$  kPa or a screening FibroTest  $\geq 0.73$  and APRI > 2.

In the absence of a qualifying liver biopsy, subjects with a screening FibroScan result that is  $\geq 12.5$  kPa and < 14.6 kPa, a FibroTest result that is  $\leq 0.72$  and an APRI > 2, or a FibroTest result that is  $\geq 0.73$  and an APRI  $\leq 2$ , should be evaluated based on the investigator's clinical judgment to determine the presence or absence of cirrhosis. The investigator will then determine and assign a fibrosis score (either F3 or F4), as shown in Table 4, which will be documented in the subject's source and recorded in the IRT system.

**Table 4. Baseline Fibrosis Stage**

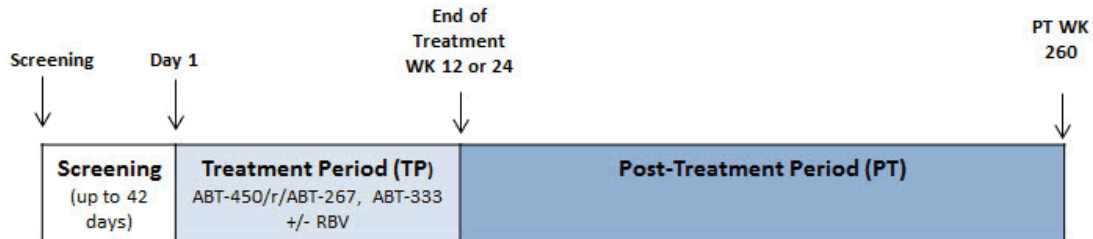
<b>Baseline Fibrosis Stage, Metavir Equivalents</b>	<b>Liver Biopsy Metavir, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec Score</b>	<b>Liver Biopsy Ishak Score</b>	<b>FibroScan (kPa)</b>	<b>FibroTest</b>
F0 – F1	0 or 1	0, 1, or 2	< 8.8	$\leq 0.48$
F2	2	3	$\geq 8.8$ to < 9.6	0.49 to 0.58
F3	3	4	$\geq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

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

The number of cirrhotic subjects (an equivalent Metavir score of F4) will be limited to less than or approximately equal to 400 subjects; the number of subjects enrolled without fibrosis or with portal fibrosis without septa (an equivalent Metavir score of F0 or F1 respectively) will be limited to 1000 subjects.

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

**Figure 1. Study Design**



### 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 designee 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 exclusionary laboratory parameter(s) must have the related panel(s) repeated (e.g., exclusionary ALT requires a repeat chemistry panel) within the same screening period and must meet all eligibility laboratory criteria on any panel that is repeated.

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)**

Subjects who meet the eligibility criteria will be enrolled to either 12 or 24 weeks of combination therapy with or without RBV as described below and [Table 5](#).

HCV GT1-infected subjects who are either treatment-naïve or treatment-experienced 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. Treatment duration of 12 weeks for HCV GT1a-infected subjects with compensated cirrhosis may be selected by the investigator where consistent with the approved local label. Subjects will receive study drug regimens according to criteria listed in [Table 5](#).

**Table 5. Treatment Regimen and Duration**

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

\* 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 in some patients where consistent with the approved local label.

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

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

All subjects will continue to return to the site on an outpatient basis through Week 12 or Week 24 depending on treatment assignment, following the study procedures identified in [Table 7](#). Subjects could also return to the site as an unscheduled study visit for additional safety visits if the investigator feels it is necessary. Sites should ensure that subjects adhere to the study visits. Sites should provide additional study drug for subjects who cannot complete their study visit per the visit schedule to 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 listed in Table 7 and as described in Section 5.4.1. Ideally, this should occur on the day of study drug discontinuation, but is recommended to be no later than 2 days after their final dose of study drugs and prior to the initiation of any other anti-HCV therapy.

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, progression of liver fibrosis, patient reported outcomes and clinical outcomes, including all-cause death, liver-related death, liver decompensation, occurrence of hepatocellular carcinoma, and liver transplantation.

### **5.1.3 Post-Treatment Period (PT)**

All subjects who receive at least one dose of study drugs will be monitored for an additional 260 weeks following the last dose of study drugs. Subjects will return to the study site as outlined in Table 7 for Post-Treatment procedures. The Post-Treatment Period will begin the day after the last dose of study drugs. Subjects could also return to the site as an unscheduled study visit for additional safety visits if the investigator feels it is necessary. Subjects who prematurely discontinue the Post-Treatment Period should return to the site for a Post-Treatment Discontinuation Visit as outlined in Table 7.

The post-treatment period will assess safety, antiviral response, progression of liver fibrosis, patient reported outcomes, and clinical outcomes, including all-cause death, liver-related death, hepatocellular carcinoma, liver decompensation and need for liver transplantation.

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.

## **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-based 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**

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

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other subject information documents), starting with Study Day 1 and for 30 days after stopping study drug, or 7 months after stopping drug if receiving RBV (or as directed by the local RBV label). (Note: Ethinyl estradiol-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 who are sexually active with female partner(s) of childbearing potential must agree to practice two effective forms of birth control (as outlined in the subject information and consent form or other subject information documents) throughout the course of the study, starting with Study Day 1 and for 30 days after stopping study drug, or for 7 months after stopping study drug if receiving RBV (or as directed by the local RBV label).
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

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**

For medications contraindicated with AbbVie's 3 DAA regimen, refer to the recommended prescribing information section of the approved local product labels in countries where the regimen contained in this study (i.e., ABT-450/r/ABT-267 and ABT-333) has received marketing authorization. If locally approved labels are not available, refer to the following Contraindicated Medication list:

Alfuzosin	Ethinyl estradiol-containing medications	Pimozide
Astemizole	Fusidic Acid	Rifampin
Carbamazepine	Gemfibrozil	Salmeterol
Cisparide	Lovastatin	Sildenafil*
Dihydroergotamine	Methylergonovine	Simvastatin
Efavirenz	Midazolam (oral)	St. John's Wort
Ergotamine	Phenobarbital	Terfenadine
Ergonovine	Phenytoin	Triazolam

\* When used for the treatment of pulmonary arterial hypertension.

Note: Not all medications contraindicated with ritonavir, ribavirin, and 3DAA regimen are listed above. Refer to the most current package inserts or product labeling of ritonavir and ribavirin for a complete list of contraindicated medications.

4. Use of known moderate or 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 in the opinion of the investigator make the subject an unsuitable candidate for this study or drug regimen.
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 IFNs 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:
$$\text{CrCl} = \frac{[(140 - \text{Age}) \times \text{Mass (in kg)} \times (0.85 \text{ if female})]}{[72 \times \text{Serum creatinine (in mg/dL)}]}$$
  - Albumin < 2.8 g/dL
  - Hemoglobin < LLN
  - Platelets < 25,000 cells per mm<sup>3</sup>
  - Total bilirubin > 3.0 mg/dL
9. Any current or past clinical evidence of Child-Pugh B or C Classification (Child-Pugh Score  $\geq$  7) or clinical history of liver decompensation such as ascites (e.g., as noted on a physical exam or imaging test), 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 and Concomitant Therapy**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

All medications will be recorded 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.

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### **5.2.3.1 Prior HCV Therapy**

Subjects may be either treatment-naïve or IFN-based therapy (IFN or pegIFN monotherapy, IFN/RBV or pegIFN/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. Subjects must be consented prior to discontinuing any prohibited medications for the purpose of meeting study inclusion criteria.

The investigator or a qualified designee should confirm that concomitant medication can be safely administered with DAAs (including ritonavir) and RBV. Some medications may require dose adjustments due to potential for drug-drug interactions. The investigator or qualified designee should review the locally approved labels for concomitant medication(s), ribavirin and ritonavir and, where available, ABT-450, ABT-267, and ABT-333 and utilize the drug-drug interactions (DDI) tool that will be provided by the sponsor to screen concomitant medications at each visit for potential DDIs with study drugs. The investigator or qualified designee should document their DDI review in the subject's source or print report and place in subject's source documents.

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 for 30 days after stopping study drug or for 7 months after stopping study drug if receiving RBV. Subjects using ethinyl estradiol-containing medications (including combination oral contraceptives) have a higher risk for elevated ALT levels. Subjects using these medications must discontinue them at least 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer. Subjects may replace the ethinyl estradiol-containing contraceptive with a progestin-only hormonal contraceptive method.

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

### **5.2.3.3 Prohibited Therapy**

In addition to the medications listed above in [Table 6](#), use of known moderate or 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 qualified designee should refer to the RBV labeling and DDI tool for a list of prohibited medications. The investigator or qualified designee should document their DDI review in the subject's source or print report and place in subject's source documents. Anti-HCV medications other than those specified in the protocol will not be allowed during the Treatment Period of the study. Some medications may require dose adjustments due to potential for drug-drug interactions.

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



**5.3 Efficacy: Pharmacokinetic and Safety Assessments/Variables**

**5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart**

**Table 7. Study Activities**

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

**Table 7. Study Activities (Continued)**

Activity	Screening	Treatment Period (TP)						End of Treatment (EOT) (Week 12 or 24) or Treatment D/C <sup>b,c</sup>	Post-Treatment (PT) Period
		Day 1 <sup>a</sup>	Week 2	Week 4	Week 12 <sup>b</sup>				
Liver Ultrasound <sup>n</sup>	X						X	X <sup>n</sup>	
Concomitant Medication Assessment <sup>o</sup>	X	X	X	X	X	X	X	X <sup>p</sup>	
Patient Reported Outcomes (SF-36v2 and FACIT-F) <sup>q</sup>		X		X	X	X	X	X	
Adverse Event Assessment	X	X	X	X	X	X	X	X <sup>p</sup>	
Study Drugs Dispensed <sup>r</sup>		X		X	X	X			
Study Drug Returned for IRT Reconciliation				X	X	X	X <sup>b</sup>		
HCV RNA Samples	X	X	X	X	X	X	X	X	
HCV Resistance Sample		X	X	X	X	X	X	X	
Liver Biopsy, FibroScan or FibroTest for liver fibrosis assessment <sup>s</sup>	X	X			X	X	X	X	
Archive Samples (Plasma and Serum)		X	X	X	X	X	X	X	
Assignment of Subject Number via IRT	X								
Enrollment		X							
Assessment of Clinical Outcomes <sup>t</sup>			X	X	X	X	X	X	

**Table 7. Study Activities (Continued)**

Activity	Treatment Period (TP)						Post-Treatment (PT) Period
	Screening	Day 1 <sup>a</sup>	Week 2	Week 4	Week 12 <sup>b</sup>	End of Treatment (EOT) (Week 12 or 24) or Treatment D/C <sup>b,c</sup>	
Clinical Assessment of Liver Decompensation		X					PT Weeks 4 <sup>d</sup> , 12, 24, 52, 104, 156, 208, 260 or PT D/C <sup>e</sup>
Total Insulin		X			X	X	X <sup>u</sup>

Wk = Week; D/C = Discontinuation

- 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 End of Treatment Week 12/ D/C visit procedures. Subjects will complete EOT Week 12 visit procedures instead of completing a TP 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 TP Week 12 Study Visit as an interim visit.
  - Study drug returned for IRT Reconciliation at TP 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 Treatment D/C visit procedures. Subjects that prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C visit procedures.
- d. Study procedures at PT Week 4 are the same as for the remaining PT visits with the exception that FibroScan and Liver ultrasound should not be conducted.
- e. Subjects will need to sign an informed consent for the study (prior to performing any screening or study-specific procedures).
- f. RBV Medication Guide where applicable/locally available.
- g. Medical history will be updated at the Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.
- h. A symptom-directed physical examination may be performed at any other visit, when necessary.
- i. Height will be measured at Screening only.

**Table 7. Study Activities (Continued)**

- j. Female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy or who are confirmed to be post-menopausal do not require pregnancy testing throughout the trial. A positive urine pregnancy test requires a confirmatory serum test. (Refer to Section 5.3.1.1 [Pregnancy Test] for additional details.) Monthly urine pregnancy testing is required for women of childbearing potential who receive RBV for seven months (or per local RBV label) after end of treatment. Females of childbearing potential that were treated with DAAs only in the Treatment Period should have urine pregnancy testing done through Post-Treatment Week 4.
- k. Urinalysis will not be conducted after the PT Week 4 Visit.
- l. Applies only to subjects with cirrhosis or suspected 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.
- m. Verify the subject has given consent for the pharmacogenetic sample. If the optional pharmacogenetic sample is not collected on Study Day 1, it may be collected at any other visit during the study.
- n. For subjects with compensated cirrhosis:
- Subjects receiving 12 weeks of treatment will have a liver ultrasound performed at the screening visit and all PT visits except PT Week 4.
  - Subjects receiving 24 weeks of treatment will have a liver ultrasound performed at the screening visit, Week 24 Visit, and all PT visits except the PT Week 4 and PT Week 12.
- For subjects without cirrhosis:
- Liver ultrasound will be performed at the screening visit, PT Week 52, PT Week 156 and PT 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.
- o. The DDI tool provided by the sponsor should be utilized to evaluate the concomitant medications.
- p. AE and concomitant medications will not be collected after the PT Week 4 Visit. Only anti-HCV medications and concomitant medications relevant to SAE of death will be collected after the PT Week 4 Visit.
- q. SF-36v2 and FACIT-F should be administered as the first study procedure at each visit and in the order listed.
- r. Study drugs dispensed at Week 12 only for subjects in the 24-week arm.
- s. 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. At sites where FibroScan is available, subjects will have FibroScan performed at Screening, End-of-Treatment Visit, and at all Post-Treatment Visits with the exception of PT Week 4.

**Table 7. Study Activities (Continued)**

- t. Clinical Outcome events that occur during the Treatment Period through PT 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 the PT 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 not be obtained at PT Week 4, 12, and 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 individual laboratory(ies).

#### **Informed Consent and RBV Information**

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. All subjects will be given the RBV Medication Guide (where applicable/locally available). Details about how informed consent will be obtained and documented are provided in Section [9.3](#).

#### **Medical History**

A complete medical history, including history of tobacco and alcohol use, will be taken at Screening. The subject's medical history will be updated at the Study Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.

#### **Physical Examination**

A complete physical examination will be performed at the Screening Visit and at Study Day 1. A symptom-directed physical examination may be performed at any other visit, when necessary.

The physical examination performed at the Study Day 1 Visit 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 and Height**

Body temperature, blood pressure, pulse and body weight will be measured at each study visit as 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 will wear lightweight clothing and no shoes during weighing.

Height will be measured only at Screening; the subject will not wear shoes.

### **12-lead Electrocardiogram**

A 12-lead resting ECG will be obtained at the Screening Visit and when clinically needed.

The ECG should be obtained prior to the blood collection.

The ECG will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will interpret, 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 assessment of the ECG tracing will be collected on case report forms, entered into the database and summarized. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

### **Pregnancy Test**

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 sent to the central laboratory for analysis.
- Pregnancy testing will be performed as specified in [Table 7](#) regardless of treatment regimen.
- Females of childbearing potential that were treated with DAAs only in the Treatment Period should have urine pregnancy testing done through Post-Treatment Week 4.
- Subjects that receive a RBV containing regimen will have pregnancy tests performed monthly throughout the Treatment Period and for a minimum of 7 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 using an unscheduled test kit 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.

### **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 must discuss any local reporting requirements to local health agencies with the subject. The site will report these results per local regulations, if necessary.

### **Clinical Laboratory Samples**

Clinical Laboratory Samples will be obtained at a minimum for the clinical laboratory tests outlined in [Table 8](#) at the visits specified in [Table 7](#). Blood samples for serum chemistry tests should be collected following a minimum 8-hour at fast on the following visits: Day 1, End of 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.

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. Depending on the location of the study site, samples may be sent to one of the following addresses:

ICON Central Laboratories, Inc.  
123 Smith Street  
Farmingdale, NY 11735  
USA

ICON Central Laboratories, Inc.  
South County Business Park  
Leopardstown, Dublin 18  
Ireland

ICON Central Laboratories, Inc.  
30 Loyang Way  
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**Table 8. Clinical Laboratory Tests**

Hematology	Clinical Chemistry	Additional Tests
Hematocrit	Blood Urea Nitrogen (BUN)	HBsAg <sup>b</sup>
Hemoglobin	Creatinine	Anti-HCV Ab <sup>b</sup>
Red Blood Cell (RBC) count	Total bilirubin <sup>a</sup>	Anti-HIV Ab <sup>b</sup>
White Blood Cell (WBC) count	Direct and indirect bilirubin	FSH (all females) <sup>b</sup>
Neutrophils	Serum glutamic-pyruvic	Urine and Serum Human
Bands, if detected	transaminase (SGPT/ALT)	Chorionic Gonadotropin
Lymphocytes	Serum glutamic-oxaloacetic	(hCG) females) <sup>c</sup>
Monocytes	transaminase(SGOT/AST)	HCV RNA
Basophils	Alkaline phosphatase	Total Insulin
Eosinophils	Sodium	IL28B <sup>b</sup>
Platelet count (estimate not acceptable)	Potassium	HCV genotype and subtype <sup>b</sup>
ANC	Calcium	Pharmacogenetic DNA
Prothrombin Time/INR <sup>a</sup>	Inorganic phosphorus	(optional)
Activated partial thromboplastin time (aPTT)	Uric acid	
Reticulocyte count	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin <sup>a</sup>	
	Chloride	
	Bicarbonate	
	Magnesium	
	Gamma-glutamyl transferase (GGT) <sup>d</sup>	
	Creatinine clearance (Cockcroft Gault calculation)	
	Alpha2-macroglobulin <sup>d</sup>	
	Haptoglobin <sup>d</sup>	
	Apolipoprotein A1 <sup>d</sup>	
	Alpha-Fetoprotein (AFP) <sup>b</sup>	
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. 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.

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

- The investigator will repeat the test to verify the out-of-range value.

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

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

### **Liver Biopsy, FibroScan or FibroTest**

At screening, 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.

FibroScan (if available) and FibroTest will be performed as indicated in [Table 7](#).

### **Child-Pugh Score and Category**

The Child-Pugh score will be calculated prior to the Day 1 Visit and documented on the Screening Visit eCRFs for cirrhotic subjects only. 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 Study Day 1 Visit for Child-Pugh assessment.

The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments) and is applicable only to subjects with cirrhosis. 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**

Parameter	Points Assigned for Observed Findings		
	1	2	3
Total bilirubin, $\mu\text{mol/L}$ (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](#).

### **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 PT 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 PT Week 4 and PT Week 12.

For subjects without cirrhosis: Liver ultrasound will be performed at the screening visit, PT Week 52, PT Week 156 and PT 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 at screening will be confirmed with CT scan or MRI during the screening period. Suspicious ultrasound lesions confirmed by CT or MRI are exclusionary.

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:

- All-cause death: death due to any cause
- Liver-related death: death as the result of a liver-related cause
- Liver decompensation: development of any of the following conditions: ascites, hepatic encephalopathy or variceal bleeding

- Liver transplantation: any subject who had a liver transplantation
- Hepatocellular carcinoma (HCC): development of HCC in any subject at any time during the study. HCC is defined by histologic confirmation or a > 1 cm mass lesion on cross-sectional imaging that meets the diagnostic criteria for HCC according to EASL guidelines.
- 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 eCRF as an AE/SAE (Section 6.0) in addition to being captured in the Clinical Outcome eCRF(s). Clinical Outcome events that occur after Post-Treatment Week 4 are considered a progression of the subject's existing liver disease and are to be recorded in the Clinical Outcome eCRFs only, except when the clinical outcome is death, in which case the AE/SAE eCRF would also need to be completed. This information may be collected over the telephone in the event the subject is unable to return to the investigative site.

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

### **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. The investigator or qualified designee should review the locally approved labels for concomitant medication(s), ribavirin and ritonavir and, where applicable, ABT-450, ABT-267, and ABT-333 and should also utilize the DDI tool that will be provided by the sponsor for potential drug interactions. The investigator or qualified designee should document their DDI review in the subject's source or print report and place in subject's source documents.

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.

### **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.

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. Subjects enrolled in the study will continue with the same subject number assigned at screening. Subject numbers will be unique 5-digit numbers and will begin with 10001.

### **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](#), study drug compliance per 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 recorded in the IRT system. Additional information regarding treatment compliance can be found in [Section 5.5.7](#).

### **HCV Genotype and Subtype**

Plasma samples for HCV genotype and subtype will be collected at Screening. Genotype and subtype will be assessed using the Versant<sup>®</sup> HCV genotype Inno-LiPA Assay, version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY). Only subjects with HCV genotype 1 infection will be allowed to enroll.

### **HCV RNA Levels**

Plasma samples for HCV RNA levels will be collected as indicated in [Table 7](#). Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0. For this assay the lower limit of quantification (LLOQ) is 15 IU/mL.

### **HCV Resistance Testing Sample**

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

### **Archive Samples**

Archive plasma and serum samples will be collected at the study visits, indicated in [Table 7](#). Archive 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) 4mL whole 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, preparation and storage will be provided by the central laboratory, the Sponsor, or its designee. Samples will be used only for IL28B testing and then destroyed.

### **Optional Pharmacogenetic Sample**

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

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

AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-450/r/ABT-267, ABT-333 (or drugs of this class) continues but no longer than 20 years.

### **5.3.1.3 Meals and Dietary Requirements**

All study drugs should be dosed together and administered with food, 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 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 mean change from baseline in FibroScan score, when available, during treatment period and post-treatment period.
- The percentage of subjects achieving SVR<sub>12</sub> and corresponding 2-sided 95% confidence interval.

### **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 tests 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.

The optional DNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to ABT-450, ABT-267, ABT-333, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, other genes believed to be related to the disease or to drug response (including IL28B). Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ABT-450, ABT-267, ABT-333, or to drugs of these classes, or the disease state. The samples may also be used for the development of diagnostic tests related to ABT-450,

ABT-267, ABT-333, drugs of these classes, or the disease state. The results of pharmacogenetic analyses may not be reported with the study summary.

## **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 yearly scheduled visit to collect the survival status only if they provide consent.

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.

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 by telephone and subsequently provide written instructions for study termination.

#### **5.4.3 Discontinuation of Subjects that Meet Virologic Failure Criteria**

The following criteria will be considered evidence of virologic failure:

- 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  $\geq$  LLOQ (defined as 2 consecutive HCV RNA measurements  $\geq$  LLOQ) at any point after HCV RNA  $<$  LLOQ

Confirmatory testing for the above criteria should be completed as soon as possible. Subjects receiving study drug treatment should remain on treatment until the virologic failure has been confirmed.

If any of the above criteria are confirmed for subjects during study drug treatment, the subject will discontinue treatment. 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 by the sponsor to the Investigator for use in this study. RBV will be provided as 200 mg tablets. RBV is dosed based on weight, for subjects with CrCl  $\geq 50$  mL/min 1000 to 1200 mg divided twice daily per local label. (For example, for subjects weighing less than 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 or more, 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  $\geq 30$  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**

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

### 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 Drug(s)

**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) Australia: Store below 25°C
Ribavirin bottles	15° to 25°C (59° to 77°F) Australia: Store below 25°C

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, the site personnel must contact the IRT and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number, assigned at the Screening Visit, throughout the study. For enrollment of eligible subjects into the study, the site will contact IRT 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 Statistics Department.

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

### 5.5.4 Selection and Timing of Dose for Each Subject

Study drug dosing will be initiated at the Day 1 Visit. ABT-450/r/ABT-267 will be dosed QD, ABT-333 and RBV (if applicable) 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) should be dosed BID, e.g., with 2 to 3 tablets taken in the morning, and 3 tablets taken in the evening based on weight.

All study drugs should be dosed together and administered with food; 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 RBV and ABT-333 should be taken 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 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. This will be documented in the IRT system. A current (running) and accurate inventory of study drug will be kept by the investigator and will include lot number, POR number, number of tablets dispensed, subject number, and date dispensed for each subject.

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

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 bottle will be noted in the IRT. 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-based therapy 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<sub>12</sub> following treatment with ABT-450/r/ABT-267 and ABT-333, with or without RBV. As such, the absence of randomization, blinding or control groups is appropriate.

### **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. FibroScan<sup>®</sup> is a validated non-invasive diagnostic test to evaluate liver disease. 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-based therapy 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. Moreover, this study population has been evaluated in the Phase 3 studies where more than 2,300 subjects received the 3-DAA 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<sub>12</sub> 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<sub>12</sub> rates (99-100%) 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<sub>12</sub> 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 has 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, and have shown high SVR<sub>12</sub> 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 (if applicable)**

The daily dose of RBV 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, 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.
- Liver transplantation: Any subject who had a liver transplantation.
- Liver decompensation: development of any of the following conditions: ascites, hepatic encephalopathy, or variceal bleeding.
- Hepatocellular carcinoma (HCC): development of HCC in any subject at any time during the study. HCC is defined by histologic confirmation or a > 1 cm mass lesion on cross-sectional imaging that meets the diagnostic criteria for HCC according to EASL guidelines.

Clinical Outcome events that occur during the Treatment Period through Post Treatment Week 4 are to be recorded and documented in 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 considered a progression of the subject's existing liver disease and are to be recorded in the Clinical Outcome eCRFs only, except when the clinical outcome is death, in which case the AE/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, or earlier as locally required.

## 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.

<b>Death of Subject</b>	An event that results in the death of a subject.
<b>Life-Threatening</b>	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.
<b>Hospitalization or Prolongation of Hospitalization</b>	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.
<b>Congenital Anomaly</b>	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
<b>Persistent or Significant Disability/Incapacity</b>	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).



**Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome**

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

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

## **6.2 Adverse Event Severity**

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

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

## **6.3 Relationship to Study Drug**

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

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

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

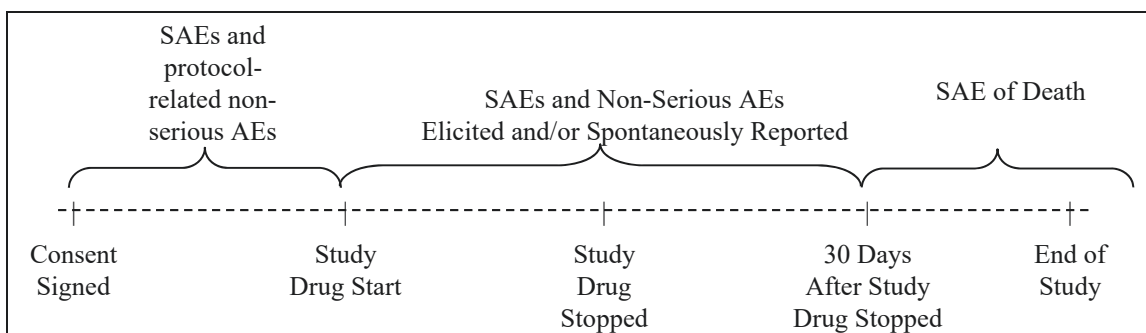
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

#### **6.4 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 drug treatment has elapsed, all adverse events and serious adverse events will be collected, whether solicited or spontaneously reported by the subject. After PT 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<sup>®</sup> system, or if RAVE is not operable, the forms should be faxed 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](mailto:PPDINDPharmacovigilance@AbbVie.com)**


For safety concerns, contact the Antiviral Safety Team at:


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


Office: +1 (847) 938-1870  
Email: [SafetyManagement\\_Virology@abbvie.com](mailto:SafetyManagement_Virology@abbvie.com)

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

Primary Study Designated Physician:

  
1 North Waukegan Road  
North Chicago, IL 60064

Office: 

Mobile: 

Fax: 

Email: 

In case of subject safety concerns or medical emergencies and the Primary Study Designated Physician is unavailable, please call the following central back-up number:

**Phone: +1 (973) 784-6402**

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

## **6.6 Pregnancy**

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

Pregnancy in a study subject must be reported to the AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects 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 risk (Section 5.4.1).

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

Subjects who discontinue study medications due to pregnancy will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.

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 resolved.

Investigators should avoid interrupting study drugs for more than 7 consecutive days. The Investigator should ensure that any study drug interruptions or RBV dose modifications and associated adverse events are promptly entered into the appropriate eCRFs.

The toxicity management guidelines below should be followed throughout the Treatment Period of the study.

### **6.7.1 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 for subjects receiving RBV or elevations of serum ALT should be managed according to the guidance in Section 6.7.4, Section 6.7.5 and Section 6.7.6 below. Grade 3 or greater abnormalities

of total bilirubin, uric acid, phosphorus, total cholesterol, triglycerides or glucose (in subjects with a history of diabetes) should be managed medically as appropriate and do not require confirmation or study drug interruption, unless deemed necessary by the investigator.

### **6.7.3 Severe Adverse Events or Serious Adverse Events**

If a subject experiences a severe adverse event or a serious adverse event that the investigator considers to have a reasonable possibility of relationship to study drug, the investigator should assess whether the adverse event can be managed medically without interruption of study drug, or whether study drugs should be interrupted until it improves. If study drugs are interrupted and restarted and the adverse event recurs, then study drugs should be permanently discontinued.

If a subject experiences a severe adverse event or serious adverse event that is considered unrelated (no reasonable possibility) to the study drugs, it is not necessary to interrupt study drugs unless an interruption is required because of the nature of the event (e.g., unable to take oral medications).

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

Severe adverse events and any associated dose interruptions (or discontinuations) should be 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 – Section 6.7.2 above.

**For subjects receiving ribavirin:**

Reductions in hemoglobin are a well characterized side effect of RBV 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
<b>Subjects with creatinine clearance <math>\geq</math> 50 mL/min</b>	
< 10 g/dL and $\geq$ 8.5 g/dL	Reduce RBV dose.* Study drugs may be continued. If hemoglobin increases to $\geq$ 10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose.
< 8.5 g/dL	Interrupt RBV. Manage the subject as medically appropriate. If hemoglobin increases to $\geq$ 8.5 g/dL, RBV may be restarted.
<b>Additional guidance for subjects with history of stable cardiac disease and creatinine clearance <math>\geq</math> 50 mL/min</b>	
Hemoglobin decrease of $\geq$ 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 RBV. Manage the subject as medically appropriate. If hemoglobin increases to $\geq$ 12 g/dL RBV may be restarted.
<b>For subjects with creatinine clearance &lt; 50 mL/min</b>	
< 10 g/dL	Interrupt RBV. Manage the subject as medically appropriate. If hemoglobin increases to $\geq$ 10 g/dL, RBV may be restarted. If creatinine clearance increases to $\geq$ 50 mL/min, refer to guidance above.

\* 1<sup>st</sup> dose reduction of RBV is by 200 mg/day or per local label. If needed, 2<sup>nd</sup> dose reduction of RBV is by an additional 200 mg/day. Subjects whose dose of RBV 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 Grade 3-4 ALT elevations have been observed in approximately 1% of subjects receiving ABT-450/r-containing regimens. If a subject experiences a post-baseline increase in ALT to  $> 5 \times$  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  $> 5 \times$  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  $> 20 \times$  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  $\geq 50$  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). RBV 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 their assigned Monitor or the following AbbVie personnel:

Primary Contact:

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

Office: [REDACTED]  
Fax: [REDACTED]

Alternate Contact:

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

Office: [REDACTED]  
Fax: [REDACTED]

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

## **8.0 Statistical Methods and Determination of Sample Size**

### **8.1 Statistical and Analytical Plans**

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<sub>12</sub>. The primary analysis will occur after all subjects have completed the study or prematurely discontinued from the study to evaluate the effect of response to treatment on clinical outcomes. For both 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<sup>®</sup> (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  $\alpha$  level of 0.05.

The intent-to-treat (ITT) population will consist of all enrolled subjects in this study (ITT-I) and companion study TOPAZ-II 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-I population will consist of all subjects enrolled in this study only who receive at least one dose of study drug. All other efficacy, safety, and demographic analyses will be performed on all subjects in the ITT-I 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 at least 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<sub>12</sub> 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-Day 1 Visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and succeeding value, the HCV RNA level will be considered undetectable or unquantifiable, respectively, at this visit for this subject. 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<sub>12</sub> 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<sub>12</sub> 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]), IFN treatment history (treatment-naïve [IFN-eligible, IFN-ineligible] or IFN-based treatment-experienced [null responder, partial responder, relapse, prior relapse/breakthrough, prior nonresponder, interferon intolerant and interferon experienced-other]), baseline HCV RNA levels [(continuous) and ( $\leq 800,000$  IU/mL or  $> 800,000$  IU/mL)], baseline HOMA-IR ( $< 3 \text{ mU} \times \text{mmol/L}^2$  or  $\geq 3 \text{ mU} \times \text{mmol/L}^2$ ), 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). 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-I population

At sites where FibroScan is available, subjects will have FibroScan<sup>®</sup> performed at Screening, End-of-Treatment Visit and throughout the Treatment and Post-Treatment Period as indicated in [Table 7](#) for the purpose of assessing changes in liver fibrosis over time.

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 Post-Treatment Period.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the COBAS<sup>®</sup> AmpliPrep/COBAS<sup>®</sup> TaqMan<sup>®</sup> HCV Test, v2.0. For this assay, the lower limit of quantification (LLOQ) is 15 IU/mL. HCV RNA results that are detectable but not quantifiable are reported as "HCV RNA is detected, less than 15 IU/mL HCV RNA".

#### **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<sub>12</sub> 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

#### **8.1.2.2 Secondary Efficacy Endpoints**

The secondary efficacy endpoints are:

- The effect of sustained virologic response and baseline fibrosis stage on longitudinal change from baseline in Fibroscan score (assessed at the end of treatment and/or post-treatment visits) will be evaluated by comparing mean change between subjects who achieve SVR<sub>12</sub> and those who do not. Point estimates and 95% confidence intervals will be provided.
- The percentage of subjects achieving SVR<sub>12</sub> (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The simple percentage of subjects achieving SVR<sub>12</sub> will be calculated and a two-sided 95% confidence interval of the percentage will be computed based on Wilson's score method.



### **8.1.2.3 Subgroup Analyses**

Subgroup efficacy analyses on clinical outcomes, liver stiffness and the percentage of subjects achieving SVR<sub>12</sub> will be performed as appropriate and useful.

### **8.1.2.4 Additional Efficacy Endpoints**

The following additional efficacy endpoints will be analyzed and summarized:

- The number and percentage of subjects meeting each and any of the following SVR<sub>12</sub> non-response categories:
  - On-treatment virologic failure (rebound or fail to suppress)
  - Relapse
  - Premature study drug discontinuation with no on-treatment virologic failure
  - Missing SVR<sub>12</sub> data
  - Other

The following analyses of patient reported outcomes (PROs) will be performed. For PRO analysis, summary statistics (n, mean, SD, minimum and maximum) will be provided at Day 1 and each applicable visit. The mean change from baseline in quality of life and fatigue to Post Treatment Week 12 and to Post-Treatment Week 24 (assessed by the Short-Form 36 Version 2 health survey (SF-36v2) questionnaires) and (The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT–F) and will be compared by appropriate baseline fibrosis stages. In particular, the comparison of the mean change from baseline to Post-Treatment Week 12 and to Post Treatment Week 24 in the SF-36 V2 Vitality scale, Mental Component Summary score, Physical Component Summary score and FACIT–F score, will be performed using ANCOVA analyses with appropriate baseline fibrosis stage as factor, and baseline PRO score and SVR<sub>12</sub> status as covariates. 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<sub>12</sub>, and who are included in the analyses described below, the sample closest in time after virologic failure with an HCV RNA level  $\geq$  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: 2 or more signature resistance-associated or emerged amino acid variants identified within a target by population sequencing, and no mixture of amino acids is detected at 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  $\geq 1000$  IU/mL that are analyzed will be compared to the baseline and appropriate prototypic reference amino acid sequences. Listings 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.

#### **8.1.5 Adverse Events**

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subject 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.

#### **8.1.6 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.

#### **8.1.7 Vital Signs Data**

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from Day 1 to each Post Baseline Visit will be summarized descriptively. Number and

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

## **8.2 Determination of Sample Size**

Assuming 4% of subjects do not achieve SVR<sub>12</sub> and assuming the 5-year event rate of the composite clinical outcome is 20% in the non-SVR<sub>12</sub> subjects, with a 75% reduction in SVR<sub>12</sub> subjects (Hazard Ratio of 0.25), then based on two-sample log rank test (using EAST 6.0), a sample size of at least 2000 subjects enrolled in TOPAZ-I and TOPAZ-II provides greater than 80% power to reject the null hypothesis of no difference between SVR<sub>12</sub> and non-SVR<sub>12</sub> subjects in the rate of clinical outcome events. Power calculations were based on a dropout rate of up to 20%.

## **8.3 Randomization Methods**

There is no randomization in this study

## **9.0 Ethics**

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

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

Any amendments to the protocol will require IEC/IRB approval, and approved by Regulatory Authority (ies), if required by local regulations, prior to implementation of any

changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

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. The subject will sign for acceptance of the optional pharmacogenetic sample on the informed consent. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The decision to allow pharmacogenetic analysis will be determined by local regulations. A blood sample for optional pharmacogenetic analysis will only be collected if the subject

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

## **10.0 Source Documents and Case Report Form Completion**

### **10.1 Source Documents**

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

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

### **10.2 Case Report Forms**

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

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

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

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

## **11.0 Data Quality Assurance**

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

## **12.0 Use of Information**

Any optional pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision-making or patient management. Hence, the investigator, the subject, nor the subject's physician (if different than the investigator) will be informed of individual

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

### **13.0 Completion of the Study**

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

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

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

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



## 14.0 Investigator's Agreement

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

Protocol Title: 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-I)

Protocol Date: 19 January 2015

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Signature of Principal Investigator

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Date

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Name of Principal Investigator (printed or typed)

## 15.0 Reference List

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## **Appendix A. Responsibilities of the Clinical Investigator**


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

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

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

**Appendix B. List of Protocol Signatories**

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Name	Title	Functional Area
		Statistics
		Clinical
		Clinical
		Clinical
		Global Drug Supply Management
		Clinical

**Appendix C. Clinical Toxicity Grades**

<b>Clinical Toxicity Grades for HCV Studies<sup>1,2</sup></b>				
	<b>GRADE 1 TOXICITY</b>	<b>GRADE 2 TOXICITY</b>	<b>GRADE 3 TOXICITY</b>	<b>GRADE 4 TOXICITY</b>
<b>HEMATOLOGY</b>				
ABSOLUTE NEUTROPHIL COUNT DECREASED	<LLN – 1500/mm <sup>3</sup> <LLN – 1.5 x 10 <sup>9</sup> /L	<1500 – 1000/mm <sup>3</sup> <1.5 – 1.0 x 10 <sup>9</sup> /L	<1000 – 500/mm <sup>3</sup> <1.0 – 0.5 x 10 <sup>9</sup> /L	<500/mm <sup>3</sup> <0.5 x 10 <sup>9</sup> /L
EOSINOPHIL COUNT INCREASED	650-1500 cells/mm <sup>3</sup>	1501-5000 cells/mm <sup>3</sup>	>5000 cells/mm <sup>3</sup>	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 x ULN	>1.5 – 2 x ULN	>2 x ULN	
LYMPHOCYTE COUNT DECREASED	<LLN – 800/mm <sup>3</sup> <LLN x 0.8 – 10 <sup>9</sup> /L	<800 – 500/mm <sup>3</sup> <0.8 – 0.5 x 10 <sup>9</sup> /L	<500 – 200 mm <sup>3</sup> <0.5 – 0.2 x 10 <sup>9</sup> /L	<200/mm <sup>3</sup> <0.2 x 10 <sup>9</sup> /L
PLATELETS DECREASED	<LLN – 75,000/mm <sup>3</sup> <LLN – 75.0 x 10 <sup>9</sup> /L	<75,000-50,000/mm <sup>3</sup> <75.0 – 50.0 x 10 <sup>9</sup> /L	<50,000-25,000/mm <sup>3</sup> <50.0 – 25.0 x 10 <sup>9</sup> /L	<25,000/mm <sup>3</sup> <25.0 x 10 <sup>9</sup> /L
PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	
WHITE BLOOD CELL COUNT DECREASED	<LLN – 3000/mm <sup>3</sup> <LLN – 3.0 x 10 <sup>9</sup> /L	<3000 – 2000/mm <sup>3</sup> <3.0 – 2.0 x 10 <sup>9</sup> /L	<2000 – 1000/mm <sup>3</sup> <2.0 – 1.0 x 10 <sup>9</sup> /L	<1000/mm <sup>3</sup> <1.0 x 10 <sup>9</sup> /L
WHITE BLOOD CELL COUNT INCREASED	10,800 – 15,000 cells/mm <sup>3</sup>	>15,000 – 20,000 cells/mm <sup>3</sup>	>20,000 – 25,000 cells/mm <sup>3</sup>	>25,000 cells/mm <sup>3</sup>
<b>CHEMISTRIES</b>				
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 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
BUN	1.25-2.5 x ULN	>2.5 -5.0 x ULN	>5 -10.0 x ULN	>10 x ULN
CALCIUM, SERUM LOW	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
CALCIUM, SERUM HIGH	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
CALCIUM, IONIZED, LOW	<LLN – 1.0 mmol/L	<1.0 – 0.9 mmol/L	<0.9 – 0.8 mmol/L	<0.8 mmol/L
CALCIUM, IONIZED, HIGH	>ULN – 1.5 mmol/L	>1.5 – 1.6 mmol/L	>1.6 – 1.8 mmol/L	>1.8 mmol/L



<b>Clinical Toxicity Grades for HCV Studies (Continued)</b>				
	<b>GRADE 1 TOXICITY</b>	<b>GRADE 2 TOXICITY</b>	<b>GRADE 3 TOXICITY</b>	<b>GRADE 4 TOXICITY</b>
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

<b>Clinical Toxicity Grades for HCV Studies (Continued)</b>				
	<b>GRADE 1 TOXICITY</b>	<b>GRADE 2 TOXICITY</b>	<b>GRADE 3 TOXICITY</b>	<b>GRADE 4 TOXICITY</b>
<b>ENZYMES</b>				
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

## **Appendix D. Protocol Amendment: List of Changes**

The summary of changes is listed in Section 1.1.

### **Specific Protocol Changes:**

#### **Section 1.0 Title Page**

**"Sponsor/Emergency Contact:"**

**Add: central back-up phone number**

Central Back-Up Phone:

+1 (973) 784-6402

#### **Section 1.2 Synopsis**

**Subsection Methodology:**

**Fifth paragraph previously read:**

The treatment duration will be 12 weeks for all subjects except HCV GT1a-infected subjects with compensated cirrhosis who are prior IFN/RBV or pegIFN/RBV null responders or nonresponders; these subjects 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; these subjects will receive treatment for 24 weeks. Treatment duration of 12 weeks for HCV GT1a-infected subjects with compensated cirrhosis may be selected by the investigator where consistent with the local approved label, in countries where marketing authorization has been granted for the regimen included in this study.

#### **Section 1.2 Synopsis**

**Subsection Methodology:**

**Add: new sixth paragraph**

HCV GT1a-infected subjects with compensated cirrhosis who were originally assigned to 12 weeks of treatment under a previous version of this protocol will be assigned to 24 weeks of treatment unless 1) the investigator determines that a 12-week duration of

therapy is appropriate based on the approved local label; 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 1.2 Synopsis**

### **Subsection Methodology:**

#### **Eighth paragraph, first sentence previously read:**

The number of cirrhotic subjects (an equivalent Metavir score of F4) will be limited to less than or equal to 400 subjects; the number of subjects enrolled without fibrosis or with portal fibrosis without septa (an equivalent Metavir score of F0 or F1 respectively) will be less than or equal to 1000 subjects

#### **Has been changed to read:**

The number of cirrhotic subjects (an equivalent Metavir score of F4) will be limited to less than or approximately equal to 400 subjects; the number of subjects enrolled without fibrosis or with portal fibrosis without septa (an equivalent Metavir score of F0 or F1 respectively) will be limited to 1000 subjects.

## **Section 1.2 Synopsis**

### **Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:**

#### **Heading "Main Inclusion:"**

#### **Criterion 2**

#### **Fourth bullet, second sub-bullet, second paragraph previously read:**

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

#### **Has been changed to read:**

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

## Section 1.2 Synopsis

### Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:

#### Heading "Main Exclusion:"

#### Criterion 1 previously read:

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 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

\* When used for the treatment of pulmonary arterial hypertension.

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.

#### Has been changed to read:

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 whichever is longer, prior to study drug administration including but not limited to:

For additional medications contraindicated with AbbVie's 3 DAA regimen, refer to the recommended prescribing information section of the approved local product labels in countries where the regimen contained in this study (i.e., ABT-450/r/ABT-267 and ABT-333) has received marketing authorization. If locally approved labels are not available, refer to the following Contraindicated Medication list:

Alfuzosin	Ethinyl estradiol-containing medications	Pimozide
Astemizole	Fusidic Acid	Rifampin
Carbamazepine	Gemfibrozil	Salmeterol
Cisapride	Lovastatin	Sildenafil*
Dihydroergotamine	Methylergonovine	Simvastatin
Efavirenz	Midazolam (oral)	St. John's Wort
Ergotamine	Phenobarbital	Terfenadine
Ergonovine	Phenytoin	Triazolam

\* When used for the treatment of pulmonary arterial hypertension.

Note: Not all medications contraindicated with ritonavir, ribavirin, and 3DAA regimen are listed above. Refer to the most current package inserts or product labeling of ritonavir and ribavirin for a complete list of contraindicated medications.

## **Section 1.3 List of Abbreviations and Definition of Terms**

### **Subsection Abbreviations**

#### **Add:**

AFP                                      Alpha-fetoprotein

## **Section 3.0 Introduction**

### **Subsection Integrated Safety Results**

#### **Fourth paragraph previously read:**

Transient asymptomatic postbaseline serum ALT elevations of  $> 5 \times$  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 postbaseline elevations in serum ALT. No ALT elevations greater than 5 times ULN were observed in subjects receiving progestins only or in subjects 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.

#### **Has been changed to read:**

Transient asymptomatic postbaseline serum ALT elevations of  $> 5 \times$  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 ethinyl estradiol-containing therapy (i.e., combination contraceptives) 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 ethinyl estradiol-containing medications is a risk factor for these postbaseline elevations in serum ALT. There was no increase in the risk of ALT elevations greater than  $5 \times$  ULN in subjects on estrogens other than ethinyl estradiol (i.e., estradiol, conjugated estrogens) or in subjects on only progestins. 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.

### **Section 3.0 Introduction**

#### **Subsection Integrated Safety Results**

**Delete: fifth paragraph**

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.

### **Section 3.0 Introduction**

#### **Subsection Integrated Safety Results**

**Seventh paragraph previously read:**

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.<sup>22-26</sup>

**Has been changed to read:**

A detailed discussion of the preclinical toxicology (including reproductive and development toxicity), metabolism, pharmacokinetics and drug-drug interactions can be found in the Investigator's Brochure for ABT-267, ABT-450, ABT-333 or prescribing information for ombitasvir/paritaprevir/r and dasabuvir in countries with marketing authorization, and product label for ritonavir and ribavirin.<sup>22-26</sup>

### **Section 3.2 Benefits and Risks**

#### **Second paragraph previously read:**

The likelihood of successfully curing HCV in compensated cirrhotics 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<sub>12</sub> following treatment for 12 and 24 weeks, respectively. Analysis of subgroups demonstrated that the difference in SVR<sub>12</sub> rates between treatment arms was due to the lower SVR<sub>12</sub> 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, suggesting that the longer duration of 24 weeks is required only for HCV GT1a null responders. SVR rates were high across all subgroups in HCV GT1b-infected subjects treated for 12 and 24 weeks. For this reason, HCV GT1a-infected subjects with compensated cirrhosis and were prior null responders to pegIFN/RBV will receive 3-DAA with RBV for 24 weeks.

#### **Has been changed to read:**

The likelihood of successfully curing HCV in compensated cirrhotics 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<sub>12</sub> following treatment for 12 and 24 weeks, respectively. Analysis of subgroups demonstrated that the difference in SVR<sub>12</sub> rates between treatment arms was due to the lower SVR<sub>12</sub> 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, suggesting that the longer duration of 24 weeks is required



only for HCV GT1a null responders. 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 this protocol HCV GT1a-infected subjects with compensated cirrhosis and who were prior null responders or non-responders to pegIFN/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 or non-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 prescribing information of some approved local labels for the 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. Treatment duration of 12 weeks for HCV GT1a-infected subjects with compensated cirrhosis may be selected by the investigator where consistent with the approved local label.

### **Section 3.2 Benefits and Risks**

#### **Add: new third 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 24 weeks of treatment unless 1) the investigator determines that a 12-week duration of therapy is appropriate based on the approved local label; 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.

**Table 4. Baseline Fibrosis Stage**  
**Last table row previously read:**

<b>Baseline Fibrosis Stage, Metavir Equivalent</b>	<b>Liver Biopsy Metavir, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec Score</b>	<b>Liver Biopsy Ishak Score</b>	<b>FibroScan (kPa)</b>	<b>FibroTest</b>
F4	4	5 or 6	≥ 12.5 to ≥ 14.6	≥ 0.73

**Has been changed to read:**

<b>Baseline Fibrosis Stage, Metavir Equivalent</b>	<b>Liver Biopsy Metavir, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec Score</b>	<b>Liver Biopsy Ishak Score</b>	<b>FibroScan (kPa)</b>	<b>FibroTest</b>
F4	4	5 or 6	≥ 14.6	≥ 0.73

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

The number of cirrhotic subjects (an equivalent Metavir score of F4) will be limited to less than or equal to 400 subjects; the number of subjects enrolled without fibrosis or with portal fibrosis without septa (an equivalent Metavir score of F0 or F1 respectively) will be less than or equal to 1000 subjects.

**Has been changed to read:**

The number of cirrhotic subjects (an equivalent Metavir score of F4) will be limited to less than or approximately equal to 400 subjects; the number of subjects enrolled without fibrosis or with portal fibrosis without septa (an equivalent Metavir score of F0 or F1 respectively) will be limited to 1000 subjects.

### Section 5.1.2 Treatment Period (TP)

#### Third paragraph, first sentence previously read:

The treatment duration will be 12 weeks for all subjects except HCV GT1a-infected prior IFN/RBV or pegIFN/RBV null responder or 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. Treatment duration of 12 weeks for HCV GT1a-infected subjects with compensated cirrhosis may be selected by the investigator where consistent with the approved local label.

**Table 5. Treatment Regimen and Duration**

#### Previously read:

Subjects		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: <ul style="list-style-type: none"> <li>• treatment-naïve</li> <li>• prior IFN/RBV or pegIFN/RBV partial responder</li> <li>• prior IFN/RBV or pegIFN/RBV relapser</li> <li>• prior IFN/RBV or pegIFN/RBV relapse/breakthrough</li> <li>• interferon intolerant</li> <li>• interferon experienced-other</li> </ul>		
	with compensated cirrhosis who are: <ul style="list-style-type: none"> <li>• prior IFN/RBV or pegIFN/RBV null responders</li> <li>• prior IFN/RBV or pegIFN/RBV nonresponder</li> </ul>	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 or with mixed subtypes.

**Has been changed to read:**

<b>Subject Population</b>	<b>Treatment Regimen*</b>	<b>Treatment Duration</b>
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

\* 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 in some patients where consistent with the approved local label.

**Section 5.2.1 Inclusion Criteria**

**Criterion 2**

**Fourth bullet, second sub-bullet, second sentence previously read:**

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

**Has been changed to read:**

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

**Table 6. Medications Contraindicated for Use with the Study Drug Regimen Previously read:**

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

\* When used for the treatment of pulmonary arterial hypertension.

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.

**Has been changed to read:**

For medications contraindicated with AbbVie's 3 DAA regimen, refer to the recommended prescribing information section of the approved local product labels in countries where the regimen contained in this study (i.e., ABT-450/r/ABT-267 and ABT-333) has received marketing authorization. If locally approved labels are not available, refer to the following Contraindicated Medication list:

Alfuzosin	Ethinyl estradiol-containing medications	Pimozide
Astemizole	Fusidic Acid	Rifampin
Carbamazepine	Gemfibrozil	Salmeterol
Cisparide	Lovastatin	Sildenafil*
Dihydroergotamine	Methylergonovine	Simvastatin
Efavirenz	Midazolam (oral)	St. John's Wort
Ergotamine	Phenobarbital	Terfenadine
Ergonovine	Phenytoin	Triazolam

\* When used for the treatment of pulmonary arterial hypertension.

Note: Not all medications contraindicated with ritonavir, ribavirin, and 3DAA regimen are listed above. Refer to the most current package inserts or product labeling of ritonavir and ribavirin for a complete list of contraindicated medications.

## **Section 5.2.2 Exclusion Criteria**

### **Criterion 4 previously read:**

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.

### **Has been changed to read:**

Use of known moderate or 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.

## **Section 5.2.2 Exclusion Criteria**

### **Criterion 6 previously read:**

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.

### **Has been changed to read:**

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 IFNs 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.

### **Section 5.2.3.2 Concomitant Therapy**

#### **Second paragraph, third sentence previously read:**

The investigator or qualified designee should review the concomitant medication(s) labels and utilize the drug-drug interactions (DDI) tool that will be provided by the sponsor to screen concomitant medications at each visit for potential DDIs with study drugs.

#### **Has been changed to read:**

The investigator or qualified designee should review the locally approved labels for concomitant medication(s), ribavirin and ritonavir and, where available, ABT-450, ABT-267, and ABT-333 and utilize the drug-drug interactions (DDI) tool that will be provided by the sponsor to screen concomitant medications at each visit for potential DDIs with study drugs.

### **Section 5.2.3.2 Concomitant Therapy**

#### **Fifth paragraph previously read:**

Prior to enrollment, subjects should agree to practice two effective methods of birth control while receiving study drugs starting with Study Day 1 for 30 days after stopping study drug or for 7 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 medications must discontinue them at least 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer. Subjects may replace the systemic estrogen-containing contraceptive with a progestin-only hormonal contraceptive method.

#### **Has been changed to read:**

Prior to enrollment, subjects should agree to practice two effective methods of birth control while receiving study drugs starting with Study Day 1 for 30 days after stopping study drug or for 7 months after stopping study drug if receiving RBV. Subjects using ethinyl estradiol-containing medications (including combination oral contraceptives) have a higher risk for elevated ALT levels. Subjects using these medications must discontinue

them at least 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer. Subjects may replace the ethinyl estradiol-containing contraceptive with a progestin-only hormonal contraceptive method.

### Section 5.2.3.3 Prohibited Therapy

#### First paragraph previously read:

In addition to the medications listed above 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.

#### Has been changed to read:

In addition to the medications listed above in Table 6, use of known moderate or 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.

### Table 7. Study Activities

Delete: row "Study Drug Returned for IRT Reconciliation"

Activity	Treatment Period (TP)						Post-Treatment (PT) Period
	Screening	Day 1 <sup>a</sup>	Week 2	Week 4	Week 12 <sup>b</sup>	End of Treatment (EOT) (Week 12 or 24) or Treatment D/C <sup>b,c</sup>	PT Weeks 4 <sup>d</sup> , 12, 24, 52, 104, 156, 208, 260 or PT D/C <sup>c</sup>
Study Drug Returned for IRT Reconciliation			X	X	X	X <sup>b</sup>	



**Table 7. Study Activities**

**Table note "j."**

**Add new last sentence to second paragraph**

Females of childbearing potential that were treated with DAAs only in the Treatment Period should have urine pregnancy testing done through Post-Treatment Week 4.

**Section 5.3.1.1 Study Procedures**

**Subsection Pregnancy Test**

**Add: new third bullet**

Females of childbearing potential that were treated with DAAs only in the Treatment Period should have urine pregnancy testing done through Post-Treatment Week 4.

**Table 8. Clinical Laboratory Tests**

**"Clinical Chemistry" column**

**Add:**

Alpha-Fetoprotein (AFP)<sup>b</sup>

**Section 5.3.1.1 Study Procedures**

**Subsection Concomitant Medication Assessment**

**First paragraph, second sentence previously read:**

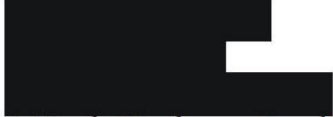
The investigator or qualified designee should review concomitant medication(s) label(s) and should also utilize the DDI tool that will be provided by the sponsor for potential drug interactions.

**Has been changed to read:**

The investigator or qualified designee should review the locally approved labels for concomitant medication(s), ribavirin and ritonavir and, where applicable, ABT-450, ABT-267, and ABT-333 and should also utilize the DDI tool that will be provided by the sponsor for potential drug interactions.


**Section 6.5 Adverse Event Reporting**

**"Primary Study Designated Physician:" address previously read:**

  
1 North Waukegan Road  
North Chicago, IL 60064

Office:   
Mobile:   
Fax:   
Email: 

**Has been changed to read:**

  
1 North Waukegan Road  
North Chicago, IL 60064

Office:   
Mobile:   
Fax:   
Email: 

**Section 6.5 Adverse Event Reporting**

**Add: new fifth paragraph and phone number**

In case of subject safety concerns or medical emergencies and the Primary Study Designated Physician is unavailable, please call the following central back-up number:

**Phone: +1 (973) 784-6402**

**Table 12. Ribavirin Dose Modification Guidelines in Management of Hemoglobin Decreases**

**Table note previously read:**

- \* 1<sup>st</sup> dose reduction of RBV is by 200 mg/day. If needed, 2<sup>nd</sup> dose reduction of RBV is by an additional 200 mg/day. Subjects whose dose of RBV is reduced to 600 mg daily receive one 200 mg tablet in the morning and two 200 mg tablets in the evening

**Has been changed to read:**

- \* 1<sup>st</sup> dose reduction of RBV is by 200 mg/day or per local label. If needed, 2<sup>nd</sup> dose reduction of RBV is by an additional 200 mg/day. Subjects whose dose of RBV is reduced to 600 mg daily receive one 200 mg tablet in the morning and two 200 mg tablets in the evening.

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

**Second paragraph, first sentence previously read:**

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design.

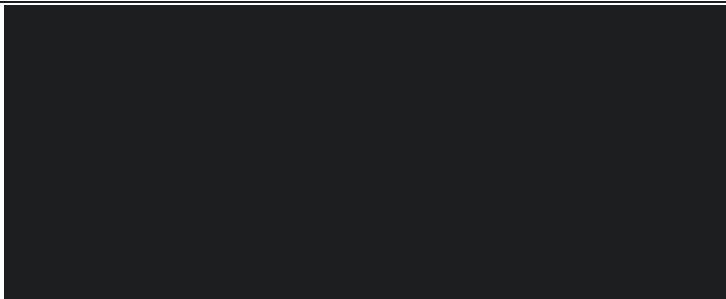
**Has been changed to read:**

Any amendments to the protocol will require IEC/IRB approval, and approved by Regulatory Authority (ies), if required by local regulations, prior to implementation of any changes made to the study design.

**Appendix B. List of Protocol Signatories**

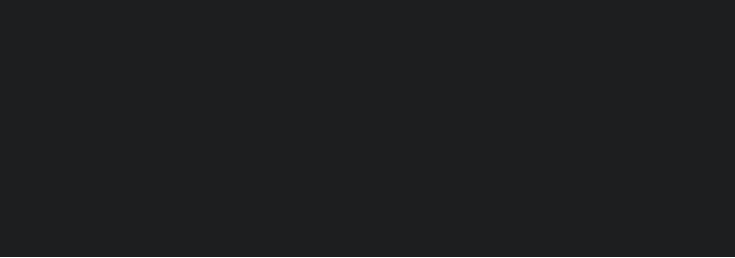
**Previously read:**

---

Name	Title	Functional Area
		Statistics
		Clinical
		Clinical
		Clinical
		Global Drug Supply Management
		HEOR
		Clinical

---

**Has been changed to read:**

Name	Title	Functional Area
		Statistics
		Clinical
		Clinical
		Clinical
		Global Drug Supply Management
		Clinical